



Europäisches Patentamt
European Patent Office
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⑪ Publication number:

0 223 420
A1

②

EUROPEAN PATENT APPLICATION

㉑ Application number: 86308087.5

㉒ Date of filing: 17.10.86

㉓ Int. Cl.4: C07D 471/04 , C07D 495/14 ,
A61K 31/47 ,
//(C07D471/04,235:00,221:00),(-
C07D495/04,333:00,235:00,221-
:00)

㉔ Priority: 18.10.85 JP 234357/85
23.05.86 JP 119681/86

㉕ Date of publication of application:
27.05.87 Bulletin 87/22

㉖ Designated Contracting States:
BE CH DE ES FR IT LI NL SE

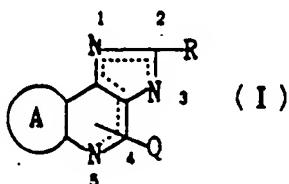
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㉚ Condensed imidazopyridine derivatives.

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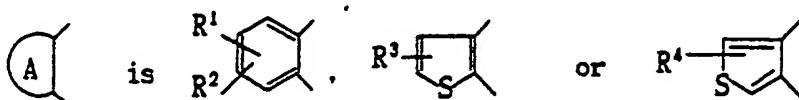


㉛ (wherein R is phenyl optionally substituted by one or two members selected from the group consisting of

trifluoromethyl, C₁-C₅ alkyl, C₁-C₅ alkoxy, C₁-C₅ alkylthio, nitro, amino C₁-C₅ alkanoylamino and C₁-C₅ alkoxy carbonyl or

5-or 6-membered heterocyclic group optionally substituted by one or two members selected from the group consisting of halogen, C₁-C₅ alkyl and C₁-C₅ alkoxy.

Q is hydrogen, C₁-C₅ alkyl, C₁-C₁₀ acyl, C₁-C₅ alkylsulfonyl or C₅-C₁₀ arylsulfonyl,



R¹, R², R³, and R⁴ each is hydrogen, halogen C₁-C₅ alkyl, C₁-C₅ alkoxy or C₁-C₅ haloalkyl,

Q is present on the nitrogen atom of the 1,3 or 5-position and the dotted line indicates the presence of three double bonds at the position of 2, 3; 3a, 3b; 4, 5 / 1, 3b; 2, 3; 3a, 4 / or 1, 2; 3a, 3b; 4, 5) or its salt, being useful as psychostimulants or anxiolytics, is provided.

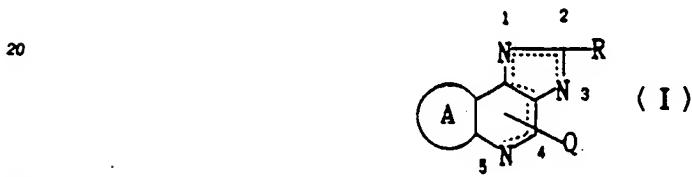
Condensed Imidazopyridine Derivatives

The present invention relates to condensed imidazopyridine derivatives. More particularly, this invention is directed to condensed imidazopyridine derivatives which have been found to be particularly effective in the treatment of depression or anxiety, to their preparation, to their use and to pharmaceutical and veterinary formulations containing the compounds.

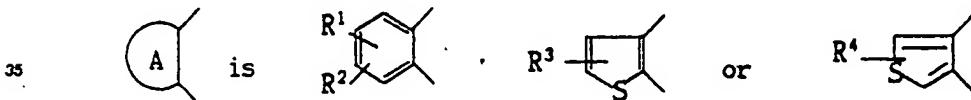
5 USSR pat. No. 509,588 discloses that 1H-2-oxo-3-phenyl-7-methyl-imidazo[4,5-c]quinoline is useful as a synthetic intermediate to biologically active materials. Abbasi et al. [Monatsh. Chem., 111, 963 (1980)] disclose 3-hydroxy-2-hydroxymethyl-8-methoxy-9-nitro-4-styryl-2H-imidazo[4,5-c]quinoline and its analogs as synthetic intermediates to biologically active materials. Further European Pat. Appln. No. 145,340 describes 2-hydroxyalkyl-1H-imidazo[4,5-c]quinolines useful as bronchodilators or antiviral agents.

10 The condensed imidazopyridine derivatives of the present invention are those having a 2-position phenyl optionally substituted by one or two members selected from trifluoromethyl, C₁-C₆ alkyl, C₁-C₅ alkoxy, C₁-C₆ alkylthio, nitro, amino, C₁-C₆ alkanoylamino and C₁-C₆ alkoxy carbonyl, or a 5-or 6-membered heterocyclic group optionally substituted by one or two members selected from halogen, C₁-C₆ alkyl and C₁-C₆ alkoxy.

15 According to the present invention there is provided a condensed imidazopyridine derivative of the formula:



wherein R is phenyl optionally substituted by one or two of trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, nitro, amino, C₁-C₆ alkanoylamino and C₁-C₆ alkoxy carbonyl or a 5-or 6-membered heterocyclic group optionally substituted by one or two of halogen, C₁-C₆ alkyl and C₁-C₆ alkoxy; Q is hydrogen, C₁-C₆ alkyl, C₁-C₁₀ acyl, C₁-C₆ alkylsulfonyl or C₆-C₁₀ arylsulfonyl;

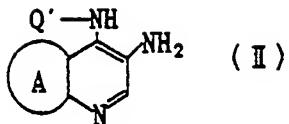


40 R¹, R², R³ and R⁴ are each independently hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₁-C₆ haloalkyl; Q is present on the nitrogen atom at the 1, 3 or 5-position; and the dotted line indicates the presence of three double bonds at the position of 2, 3; 3a, 3b; 4, 5 / 1, 3b; 2, 3; 3a, 4 / 1, 2; 3a, 3b; 4, 5). The invention further relates to compounds of formula I which are acid addition salts thereof.

45 The compounds of the present invention have an excellent psychotropic activity such as psychostimulant or anxiolytic activity with no undesirable side effects. Accordingly, the compound may be used in a psychotropic formulation comprising as an active ingredient 0.1 to 95% by weight of a compound of the formula (I) associated with at least one carrier, diluent or excipient therefor.

The compounds of the invention may be used in the treatment of a patient suffering from depression or anxiety by the administration to the patient of a pharmacologically effective amount of a compound of the formula (I).

50 The invention further provides a process for preparing a compound of the formula (I) which comprises reacting a compound of the formula:



5 wherein Q' is hydrogen or C₁-C₆ alkyl, and

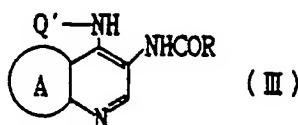
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is as defined above with an acylating agent to give a compound of the formula:

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wherein

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30 , Q' and R each is as defined above and cyclizing the compound (III) and then Q' is hydrogen, applying the cyclized product to alkylation, acylation or sulfonylation, if necessary.

The term "C₁-C₆ alkyl" herein employed may include a straight or branched saturated aliphatic hydrocarbon radical such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl or 1-methylisobutyl.

35 The term "C₁-C₆ alkoxy" may include an alkoxy group containing a C₁-C₆ alkyl moiety such as methoxy, ethoxy, propoxy, isopropoxy, butoxy and pentyloxy.

The term "C₁-C₆ alkylthio" may include an alkylthio group containing a C₁-C₆ alkyl moiety such as methylthio, ethylthio, propylthio, butylthio isobutylthio and neopentylthio.

40 The term "C₁-C₆ alkanoylamino" includes formylamino, acetylamino, propionylamino, butyrylamino, valerylamino and isovalerylamino.

The term "C₁-C₆ alcoxycarbonyl" includes methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and pentyloxycarbonyl.

45 The term "5-or 6-membered heterocyclic group" includes isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, thiadiazolyl, oxadiazolyl, thiényl, furyl and pyridyl.

The term "C₆-C₁₀ acyl" includes C₆-C₁₀ alkanoyl such as formyl, acetyl, propionyl, butyryl, valeryl or isovaleryl and C₆-C₁₀ aroyl such as benzoyl, toluoyl or propylbenzoyl.

The term "C₁-C₆ alkylsulfonyl" includes methylsulfonyl, ethylsulfonyl, propylsulfonyl, isobutylsulfonyl and pentylsulfonyl.

50 The term "C₆-C₁₀ arylsulfonyl" includes phenylsulfonyl, tolylsulfonyl, xylylsulfonyl and naphthylsulfonyl.

The term "C₁-C₆ haloalkyl" includes fluoromethyl, chloroethyl, bromopropyl, iodobutyl and trifluoromethyl.

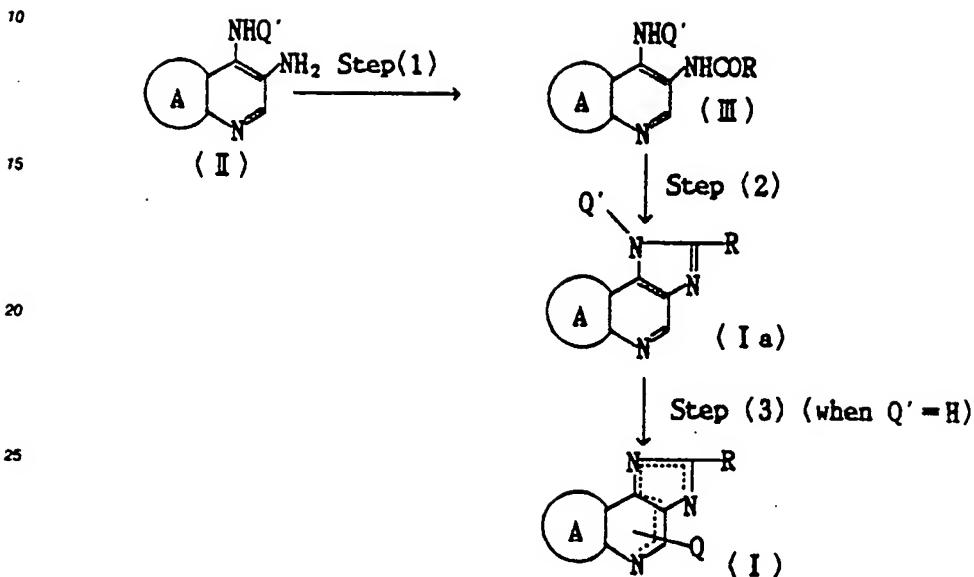
The term "halogen" includes fluorine, chlorine, bromine and iodine.

The process for preparing the compound (I) may be shown by the scheme as follows:

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SCHEME

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(wherein Q' is hydrogen or C₁-C₅ alkyl, and
are as defined above).

Step (1)

The amide (III) can be prepared by reacting the diamine (II) with an acylating reagent. The reaction may be performed at a comparatively lower temperature (e.g. -10 to 5°C) generally in an appropriate solvent, using an acylating agent containing a necessary acyl group. The solvent includes illustratively dimethylformamide, acetonitrile, chloroform, hexamethylphosphoramide, ether, tetrahydrofuran or mixtures thereof. The

acylating reagent refers to an acid halogenide such as acid chloride or acid bromide; a mixed acid anhydride; a mixture of carboxylic acid with thionyl chloride; a mixture of carboxylic acid with a condensing agent such as DCC or polyphosphoric acid.

5

Step (2)

The compound (Ia) can be prepared by heating the amide (III) in a solvent at a temperature from about 50°C to 250°C, preferably 100°C to 250°C in the presence or absence of cyclizing agent such as 10 polyphosphoric acid, polyphosphoric ester, sulfuric acid, acetic acid or phosphorus pentoxide. The solvent includes illustratively hexamethylphosphoramide, diphenyl ether, glycerin triethyl ether, butyl ether, isoamyl ether, diethylene glycol, triethylene glycol or Dowtherm A (Dow Chemical Co.).

15 Step (3)

As necessary, the compound (Ia) ($Q' = \text{Hydrogen}$) may be subjected to alkylation, acylation or sulfonylation. The reaction may be performed with an alkylating, acylating or sulfonylating agent in an appropriate solvent in the presence of a base such as alkali metal hydride. (e.g. sodium hydride, potassium 20 hydride) or alkali metal alkoxide (e.g. sodium methoxide, potassium ethoxide, sodium isopropoxide) at a temperature of 30 to 120°C. The alkylating agent includes alkyl halide such as methyl iodide, ethyl bromide, propyl chloride or butyl iodide and dialkyl sulfate such as dimethyl sulfate or diethyl sulfate. The acylating agent includes acyl halide such as acetyl chloride, propionyl bromide, butyryl chloride or benzoyl chloride and acid anhydride such as acetic anhydride or propionic anhydride. The sulfonylating agent 25 includes mesyl chloride, butylsulfonyl chloride and tosyl chloride. As solvents there are exemplified tetrahydrofuran, dioxane, diglyme, dimethylformamide, chloroform and ethanol.

The diamine (II) usable as a starting material can be prepared, as shown below, in accordance with the methods of G. B. Bachman et al., J. Am. Chem. Soc., 69, 365 (1947) and A. R. Surrey et al., J. Am. Chem. Soc., 73, 2413 (1951).

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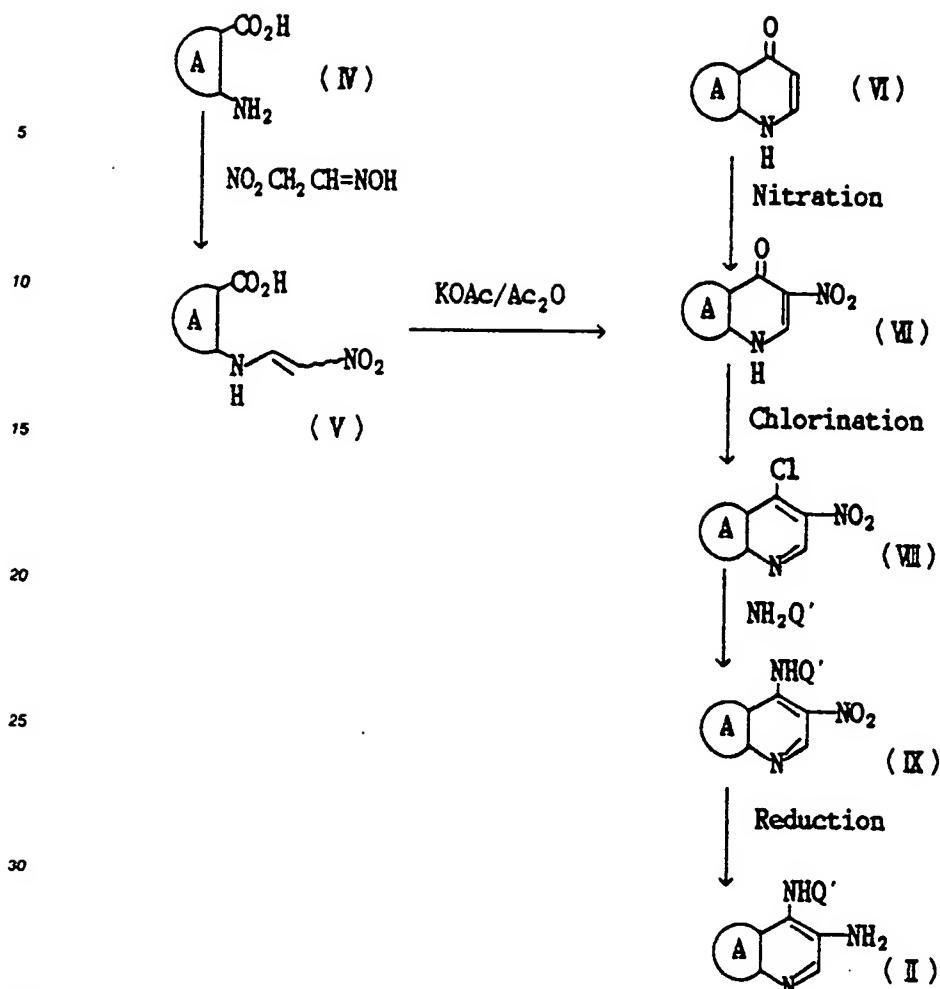
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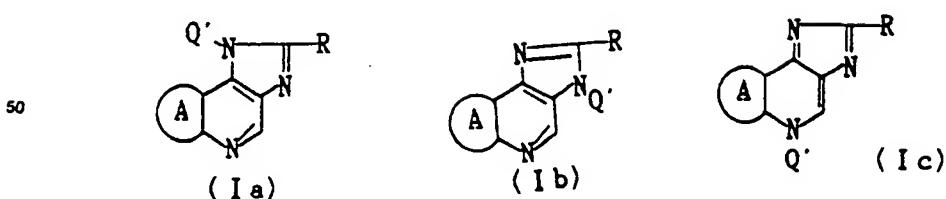
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and Q' are as defined above.)

The compound (I) includes the following three compounds (I^a, I^b and I^c):

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(wherein , Q' and R are as defined above).

The compound (I) can be converted into its physiologically acceptable acid addition salts. Such acids illustratively include an inorganic acid such as hydrochloric acid, sulfuric acid, phosphoric acid or nitric acid and an organic acid such as acetic acid, maleic acid, malic acid, citric acid, lactic acid, succinic acid or methanesulfonic acid.

5 The invention further relates to a pharmaceutical or veterinary formulation comprising a compound of formula (I) formulated for pharmaceutical or veterinary use, respectively. The formulation may be in unit dosage form and/or may further comprise a pharmaceutically or veterinarily acceptable carrier, diluent or excipient.

10 The compound of formula (I) and its salts may be of general use in the treatment of disease. The invention includes the use of the compound of formula (I) and its salts in the manufacture of a medicament for the treatment of anxiety or depression.

15 The compounds (I) or acceptable acid addition salts thereof have a high affinity to benzodiazepine receptors, and they are useful as psychotropics agents such as psychostimulants or anxiolytics.

17 The compounds (I) can be administered orally or parenterally to human beings or other animals. They can be formulated as tablets, capsules, pills, granules, injections, suppositories, and syrups. As acceptable carriers, diluents or excipients there are exemplified lactose, sucrose, wheat starch, potato starch, magnesium stearate, gelatin, methyl cellulose, agar, water, and the like. As necessary, appropriate stabilizers, emulsifiers, spreaders, buffers and other adjuvants can be added. Appropriate daily dosage of the compound (I) is 0.1 to 500 mg in oral route and 0.1 to 300 mg in injection.

20 The present invention may be explained in more detail by the following non-limiting Examples, Referential Examples and Formulations.

The abbreviations used in Examples, Referential Examples and Tables have the following meanings.

HMPA : Hexamethylphosphoramide

Me : Methyl

25 Et : Ethyl

PPA : Polyphosphoric acid

MeCN : Acetonitrile

MeOH : Methanol

EtOH : Ethanol

30 Et₂O : Ether

AcOEt : Ethyl acetate

AcOH : Acetic acid

DMF : Dimethylformamide

(d) : Decomposition

35 When Q is hydrogen, the compound (Ia) and (Ib) being a tautomer of each other will be named conveniently as said formula (Ia).

For example, 2-(3-trifluoromethylphenyl)-1H-imidazo[4,5-c]quinoline C₁ (Example 1) may be also named as 2-(3-trifluoromethylphenyl)-3H-imidazo[4,5-c]quinoline.

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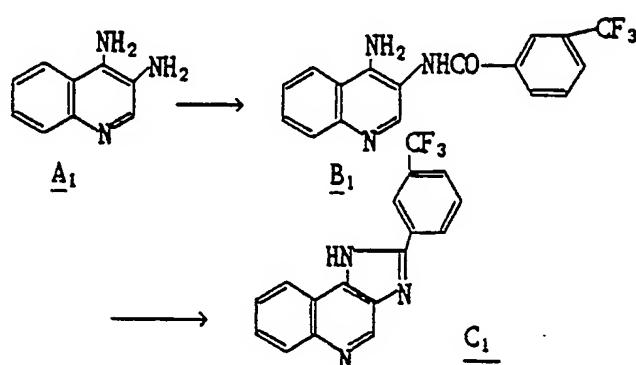
Example 1

2-(3-Trifluoromethylphenyl)-1H-imidazo[4,5-c]quinoline C,

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To a solution of 500 mg of 3-trifluoromethylbenzoic acid in 6 ml of anhydrous hexamethylphosphoramide (HMPA) and 0.6 ml of anhydrous acetonitrile is added dropwise 305 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring at the same temperature for 30 minutes, 380 mg of 3,4-diaminoquinoline is added and stirred at 0 -5°C for 3 hours. The mixture is diluted with ice-water and neutralized with saturated aqueous sodium bicarbonate. The resulting crystals are filtered, washed with water, and dried to give 780 mg of 4-amino-3-(3-trifluoromethylbenzoylamino)quinoline B, as a crude product. It is suspended in 15 g of polyphosphoric acid and heated at 120°C for 4 hours with stirring. The mixture is poured into ice-water and neutralized with 1N sodium hydroxide. The resulting solid is filtered, 10 washed with water and dried. It is chromatographed on silica gel with chloroform -methanol (10:1 v/v) as eluent, yielding 350 mg (47%) of C₁ as colorless crystals.
 m.p. 254 -256°C (from ethyl acetate)
 Anal.Calcd.(%)(for C₁₁H₁₀N₂F₃)
 : C, 65.18; H, 3.22; N, 13.41; F, 18.19.
 15 Found (%) : C, 64.74; H, 3.54; N, 13.20; F, 18.30.

Example 2-3

20 According to the method illustrated by Example 1, the compounds C₂ and C₃ are prepared under the conditions shown in Table 1. Table 3 shows the physical properties of these compounds.

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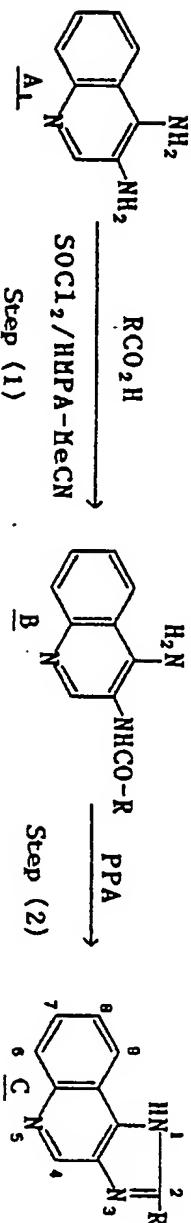
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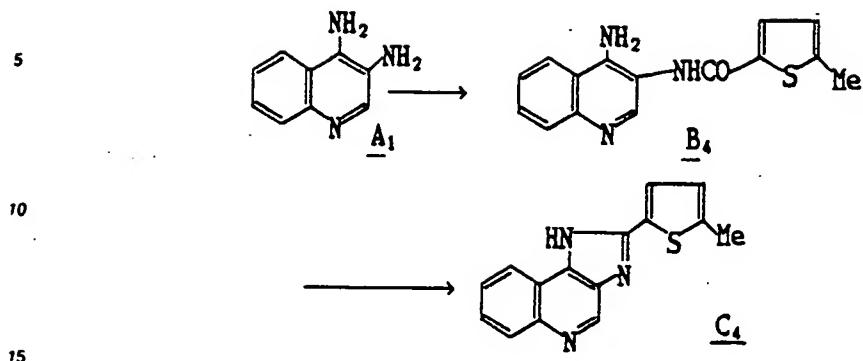
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Table 1

Ex. No.	R	Step (1)						Step (2)			
		ROCO ₂ H	SOCl ₂	HMPA-MeCN	Compd. A, (mL)	Reac- tion Time (hr)	PPA	Temp. (°C)	Reac- tion Time (hr)	Yield (g)	Yield (%) from Compd. A, No.
1		420	305	6	0.6	380	3.5	15	120	7.5	365
2											54
3		370	305	6	0.6	380	3.5	12	135	4	480
											C,

Example 4

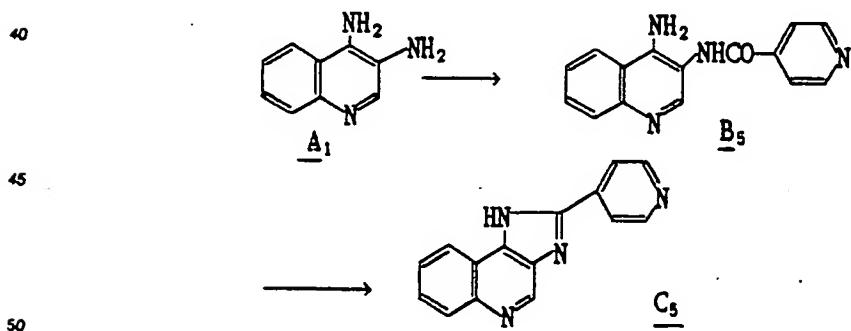
2-(5-Methylthien-2-yl)-1H-imidazo[4,5-c]quinoline C₁



To a solution of 555 mg of 5-methylthiophene-2-carboxylic acid in 9 ml of anhydrous hexamethylphosphoramide and 0.9 ml of anhydrous acetonitrile is added dropwise 455 mg of thionyl chloride at -5 -
20 0°C under nitrogen. After stirring at the same temperature for 30 minutes, 570 mg of 3,4-diaminoquinoline is added and stirred at 0 -5°C for 4 hours. The same work-up as described in Example 1 gives 900 mg of
25 4-amino-3-(5-methylthien-2-ylcarbonylamino)quinoline B₄ as a white solid. It is suspended in 15 g of polyphosphate ester and heated at 125°C with stirring for 3 hours. The mixture is diluted with ice-water and neutralized with 1N sodium hydroxide and extracted with ethyl acetate. The extract is washed with water
30 and saturated sodium chloride, dried over magnesium sulfate, and evaporated. The residue is chromatographed on silica gel with chloroform -methanol (10:1 v/v) as eluent to give 456 mg (48%) of C₄ as pale yellow crystals.
m.p. 293 -295°C (dec.) (from ethanol)
Anal. Calcd. (%) (for C₁₅H₁₄N₂S) : C, 67.90; H, 4.18; N, 15.84; S, 12.08.
35 Found (%) : C, 68.16; H, 4.25; N, 15.76; S, 11.63.

Example 5

35 2-(Pyridin-4-yl)-1H-imidazo[4,5-c]quinoline C₅



To a solution of 325 mg of isonicotinic acid in 8 ml of anhydrous hexamethylphosphoramide and 0.8 ml of anhydrous acetonitrile is added dropwise 305 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring for 45 minutes, 380 mg of 3,4-diaminoquinoline A₁ is added and the mixture is stirred at 0°C for 4.5 hours. The same work-up as described in Example 1 gives 560 mg of crude crystals of B₅. It is dissolved in 10 ml of acetic acid and refluxed for 4 hours. The mixture is concentrated under reduced pressure and mixed with ice-water and neutralized with saturated sodium bicarbonate. The resulting crystals are filtered

and dried to yield 510 mg (87%) of C₅ as white crystals.

m.p. 270 -272°C (from ethyl acetate - methanol)

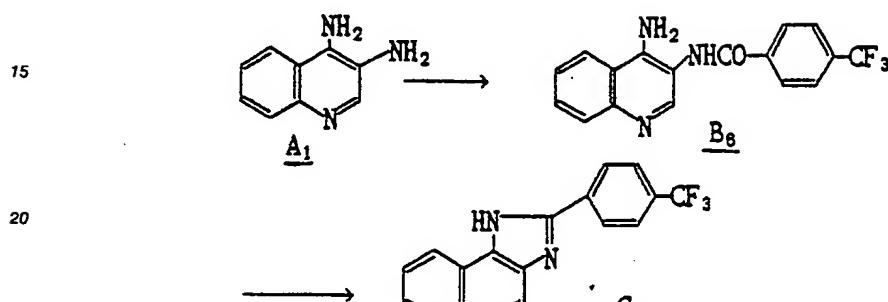
Anal. Calcd. (%) (for C₁₅H₁₂N₂)

C 73.16 H 4.09 N 22.75

⁵ Found (%): C 72.79; H 4.20; N 22.37.

Example 6

19 2-(4-Trifluoromethylphenyl)-1*H*-imidazo[4,5-*c*]quinoline C.



To a solution of 395 mg of 4-trifluoromethylbenzoic acid in 5 ml of anhydrous hexamethylphosphoramide and 0.5 ml of anhydrous acetonitrile is added dropwise 240 mg of thionyl chloride at -5 - 0°C under nitrogen. After stirring at the same temperature for 30 minutes, 300 mg of 3,4-diaminoquinoline A₁ is added and stirred at 0 - 5°C for 4 hours. The same work-up as described in Example 1 gives 605 mg of the crude crystals of B₄. It is suspended in 10 ml of hexamethylphosphoramide and 2.5 ml of acetic acid, and stirred at 155°C for 15 minutes under nitrogen. The cooled mixture is diluted with water and neutralized with saturated aqueous sodium bicarbonate. The resulting solid is chromatographed on silica gel with chloroform -methanol (10:1 v/v) as eluent to give 440 mg (75%) of C₆ as white crystals.

35 m.p.: >340°C (from ethanol)

Anal. Calcd. (%) (for C₁₇H₁₀N₃F₃)

: C. 65.18; H. 3.22; N. 13.41; E. 18.19.

Found (%) : C. 64.95; H. 3.44; N. 13.24; E. 18.10

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Example 7-93

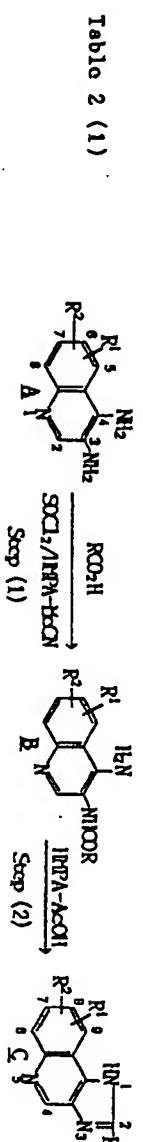
According to the method illustrated by Example 6, Compounds C₇, C₁₁ are prepared under the conditions shown in Table 2. Table 3 shows the physical properties of these compounds.

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Table 2 (1)



Ex. No.	R	Step (1)					Step (2)					Compd. C				
		RCO ₂ H (mg)	SOCl ₂ , HMPA - CHCl ₃ (mL)	R ¹	R ²	Compd. (mg)	Reaction time (hr)	HMPA - AcOH (mL)	Temp. (°C)	Reac- tion Time (min)	Yield (%)	Yield (%) from Compd. A	No.			
7		670	710	12	1.2	H	H	760	3.5	20	5	155	100	875	73	C, C ₁₁
8		520	305	6	0.6	H	H	380	3.5	12	3	150	35	560	73	C ₁₁
9		420	.305	6	0.6	H	H	380	4.5	12	3	155	30	390	57	C, C ₁₁
10		325	305	6	0.6	H	H	380	4.5	2	4	140	120	315	53	C ₁₁
11		335	305	6	0.6	H	H	380	4.5	10	2.5	150	30	365	61	C ₁₁
12		295	305	6	0.6	H	H	380	4.5	2	4	140	120	210	37	C ₁₁
13		315	240	5	0.5	H	H	300	4.5	8	2	150	30	230	44	C ₁₁

Table 2 (2)

14		320	305	6	0.6	H	H	380	3.5	10	2.5	145	15
15		280	200	5	0.5	6-Cl	H	300	4.5	8	2	150	60
16		240	200	5	0.5	6-Cl	H	300	4.5	8	2	155	30
17		295	305	6	0.6	H	H	380	4.5	10	2.5	150	30
18		350	240	5	0.5	H	H	300	4.5	8	2	150	30
19		370	240	5	0.5	H	H	300	4.5	10	2.5	150	15
20		290	240	5	0.5	H	H	300	4.5	8	2	165	15
21		290	240	5	0.5	H	H	300	4.5	4	4	150	90
22		325	240	5	0.5	H	H	300	4.5	8	2	155	45
23		330	240	5	0.5	H	H	300	4.5	8	2	165	30
24		315	240	5	0.5	H	H	300	4.5	12	4	165	60

Table 2 (3)

25		380	305	6	0.6	H	H	380	4.5	10	2.5	155	10	350	55	C,,
26		375	240	5	0.5	H	H	300	4.5	12	3	155	30	255	45	C,,
27		425	305	6	0.5	H	H	380	4.5	8	2	155	10	520	77	C,,
28		380	210	5	0.5	H	H	300	3.5	8	2	165	30	280	49	C,,
29		380	240	5	0.5	H	H	300	3.5	8	2	165	20	390	68	C,,
30		350	240	5	0.5	H	H	300	5.5	10	2.5	165	60	460	84	C,,
31		330	240	5	0.5	H	H	300	4.5	4	4	145	45	480	91	C,,
32		330	240	5	0.5	H	H	300	4.5	4	4	140	30	470	89	C,,
33		330	240	5	0.5	H	H	300	3.5	6	4	155	30	430	81	C,,
34		465	305	6	0.6	H	H	380	4.5	10	0	225	30	565	79	C,,
35		265	240	5	0.5	7-C1	H	365	4.5	8	2	160	30	380	71	C,,

Table 2 (4)

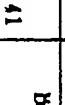
36		290	240	5	0.5	7-Cl	H	365	4.5	8	2	160	15	385	69	C ₁₁
37		375	305	6	0.5	H	H	380	4.5	10	2.5	160	45	540	85	C ₁₁
38		295	240	5	0.5	7-Cl	H	365	4.5	8	2	165	40	400	71	C ₁₁
39		295	240	5	0.5	7-Cl	H	365	4.5	8	2	170	10	380	67	C ₁₁
40		290	240	5	0.5	6-F	H	330	4.5	8	2	165	10	425	81	C ₁₁
41		295	240	5	0.5	6-F	H	330	4.5	8	2	160	15	390	74	C ₁₁
42		206	181	4	0.4	7-Me	H	250	4	5.7	1.4	180	30	323	83	C ₁₁
43		228	181	4	0.4	7-Me	H	250	5	6	1.5	180	60	325	81	C ₁₁
44		214	192	5	0.5	6-Cl	7-Cl	343	2.5	8	2	170	40	314	65	C ₁₁
45		1770	1250	20	2	H	H	2000	3	36	9	180	40	2940	93.6	C ₁₁
46		274	220	4	0.4	H	H	280	4	6	1.5	180	30	338	73	C ₁₁

Table 2 (5)

Table 2 (6)

58		249	250	4 0.4	H	H	318	4	6 1.5	180	20	382	82	C..
59		193	194	4 0.4	7-Cl	H	300	3.5	4 1	180	15	307	75	C..
60		210	211	4 0.4	7-F	H	300	3	4 1	180	20	321	76	C..
61		280	250	4.6 0.5	H	H	318	3.5	5.6 1.4	180	15	326	70	C..
62		198	177	4 0.4	7-F	H	250	3	4.5 1.1	180	20	268	72	C..
63		244	197	4 0.4	H	H	250	4	5 1.2	180	30	317	76	C..
64		220	177	4 0.4	7-F	H	250	5	4.8 1.2	180	20	275	70	C..
65		221	198	4 0.4	6-F	H	280	3.5	5.2 1.3	185	25	378	91	C..
66		203	182	4 0.4	7-Cl	H	280	5	4.8 1.2	185	20	291	72	C..
67		229	181	4 0.4	H	H	230	3.5	5 1.2	180	15	303	81	C..
68		229	181	4 0.4	H	H	230	3.5	5 1.2	180	25	318	83	C..

5 10 15 20 25 30 35 40 45 50 55

Table 2 (7)

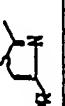
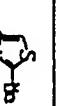
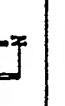
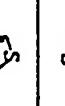
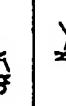
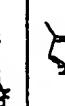
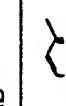
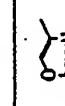
69		223	197	4	0.4	H	H	250	4	4.4	1.1
70		225	197	4	0.4	H	H	250	4.5	4.8	1.2
71		336	268	4	0.4	H	H	340	5	5	1.2
72		298	238	4	0.4	H	H	300	4	4	1
73		303	268	4	0.4	H	H	340	6	4	1
74		303	268	4	0.4	H	H	340	4	4	1
75		330	305	6	0.6	H	H	380	4.5	14	3.5
76		330	305	6	0.6	H	H	380	4.5	6	1
77		670	610	10	1	H	H	760	4.5	12	3
78		303	268	4	0.4	H	H	340	4	4	1
79		193	194	4	0.4	8-Cl	H	300	3	4	1

Table 2 (8)

80		246	248	4	0.4	8-F	H	350	3	4	1	180	25	303	60	C..
81		562	565	7	0.7	6-F	H	800	5	8	2	180	25	862	75.4	C..
82		244	245	4	0.4	6-OHg	H	370	4	5	1.2	180	30	403	77.4	C..
83		497	500	7	0.7	7-F	H	708	5	0	9	118	60	679	808	C..
84		249	250	4	0.4	8-F	H	354	4	4.8	1.2	180	30	335	77.8	C..
85		249	250	4	0.4	7-Me	H	354	4	4	1	180	35	390	78.0	C..
86		199	199	4	0.4	7-CF ₃	H	360	3.5	4	1	180	30	376	78.0	C..
87		374	375	5	0.5	5-F	H	531	3.5	4	1	180	30	367	48.2	C..
88		282	250	4	0.4	5-F	H	354	4	4.8	1.2	180	50	432	80.3	C..
89		200	177	4	0.4	8-F	H	250	4	5.6	1.4	180	35	312	87.6	C..
90		245	345	4	0.5	5-Cl	H	312	3.0	7	2	160	40	312	72	C..

0 223 420

Table 2 (9)

91		278	344	4	0.5	5-Cl	H	313	2.3	6	2	160	40	268	58	C,,
92		309	331	4	0.5	5-Cl	H	311	3.0	6	2	163	45	346	72	C,,
93		315	283	5	0.5	5-?	H	400	4	4	1	180	40	303	50	C,,

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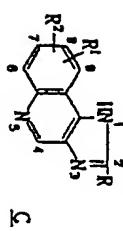
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Table 3 (1)



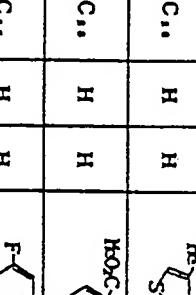
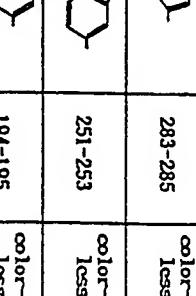
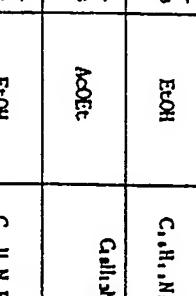
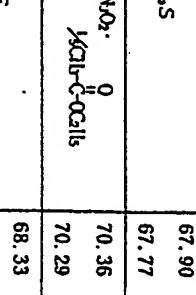
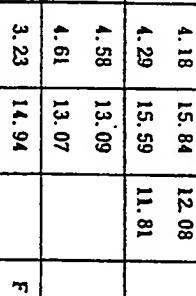
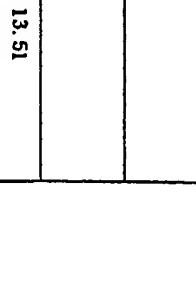
Compd. No.	R'	R'	R	m. p. (°C)	Appea- rance	Solvent for Crystallin.	Elementary Analysis (%)				Up : Calcd. Down : Found
							C	H	N	S	
C ₁	H	H		296-298	light yellow	EtOH	C ₁₁ H ₁₁ N ₂ SCl	58.85	2.82	14.71	11.22 C1 12.41
C ₂	H	H		300-301	colorless	EtOH	C ₁₁ H ₁₁ N ₂ F	58.86	3.22	14.40	11.22 C1 12.34
C ₃	H	H		304-305	colorless	EtOH	C ₁₁ H ₁₁ N ₂ S	72.99	3.83	15.96	F 7.22
C ₄	H	H		225-227	colorless	AcOEt-n-hexane	C ₁₁ H ₁₁ N ₂ SCl	72.90	4.13	15.75	F 7.17
C ₅	H	H		286-288	colorless	EtOH	C ₁₁ H ₁₁ N ₂ SCl	66.91	3.61	16.72	12.76
C ₆	H	H		247-249	colorless	EtOH	C ₁₁ H ₁₁ N ₂ S	66.94	3.55	16.61	12.52
C ₇	H	H		280-282	colorless	EtOH-AcOEt	C ₁₁ H ₁₁ N ₂ S	52.52	2.20	13.12	10.01 C1 22.14
C ₈	H	H		257-258	colorless	AcOEt	C ₁₁ H ₁₁ N ₂ O	52.23	2.58	13.00	9.95 C1 22.05
C ₉	H	H		292-293	colorless	MeOH-AcOEt	C ₁₁ H ₁₁ N ₂ O	74.17	4.76	15.26	
								73.80	4.90	14.84	

Table 3 (2)

C.,	H	H	<chem>c1ccccc1</chem>	298-300	colorless	EtOH	C ₆ H ₅ N,	78.35	4.32	17.13		
C.,	8-Cl	H	<chem>CC1=CSC=C1</chem>	315-316	colorless	EtOH-AcOEt	C ₆ H ₄ NSCl ₂ , KAl(C ₂ O ₄) ₂	52.57	2.39	12.77	9.74	Cl 21.55
C.,	8-Cl	H	<chem>Fc1ccccc1</chem>	316-318	colorless	EtOH-AcOEt	C ₆ H ₄ N,ClF	64.55	3.05	14.11	Cl 11.91, F 6.38	
C.,	H	H	<chem>CC1=CC(F)=CC1</chem>	290-291(d)	colorless	EtOH-AcOEt	C ₆ H ₅ N,O	64.54	3.20	14.10	Cl 11.83, F 6.27	
C.,	H	H	<chem>CC1=CC(F)=CC1</chem>	325-326	colorless	EtOH	C ₆ H ₅ N,S	71.48	3.86	17.86		
C.,	H	H	<chem>CC1=CC(F)=CC1</chem>	>340	colorless	EtOH	C ₆ H ₅ N,O-KH ₂ O	71.47	4.01	17.80		
C.,	H	H	<chem>CC1=CC(F)=CC1</chem>	291-293	colorless	EtOH-AcOEt	C ₆ H ₅ N,F	69.44	4.86	18.00		
C.,	H	H	<chem>CC1=CC(F)=CC1</chem>	259-260	colorless	EtOH-AcOEt	C ₆ H ₅ N,F	72.99	3.83	15.96	F 7.22	
C.,	H	H	<chem>CC1=CC(F)=CC1</chem>	199-201	colorless	AcOEt	C ₆ H ₅ N,Cl	72.62	3.88	15.83	F 7.28	
C.,	H	H	<chem>CC1=CC(F)=CC1</chem>	305-306	light yellow	EtOH-AcOEt	C ₆ H ₅ N,SCl	68.70	3.60	15.02	Cl 12.67	
C.,	H	H	<chem>CC1=CC(F)=CC1</chem>	233-235	colorless	AcOEt	C ₆ H ₅ N,O	58.58	2.82	14.71	11.22	Cl 12.41
								58.58	3.16	14.43	10.95	Cl 12.52
								74.17	4.76	15.26		
								74.02	4.78	14.97		

5 10 15 R 20 30 35 40 45 50 55

Table 3 (3)

C., H	H		283-285	colorless	EtOH	C ₁₀ H ₁₁ N ₂ S	67.90	4.18	15.84	12.08	
C., H	H		251-253	colorless	AcOEt	C ₆ H ₃ N ₃ O ₄ KOBz-C(=O)OCbz	70.36	4.58	13.09		
C., H	H		194-195	colorless	EtOH	C ₆ H ₃ N ₃ F ₂	68.33	3.23	14.94	F 13.51	
C., H	H		265-267	colorless	EtOH	C ₆ H ₃ N ₃ O ₄ /H ₂ O	70.29	5.00	13.66		
C., H	H		291-292	colorless	EtOH	C ₆ H ₃ N ₃ O ₄	70.26	5.07	13.66		
C., H	H		>340	Yellow	DMF	C ₆ H ₃ N ₃ O ₄ ·H ₂ O	71.17	4.94	13.80		
C., H	H		248-250	colorless	EtOH	C ₆ H ₃ N ₃ F ₂	65.48	3.74	18.91		
C., H	H		224-226	colorless	EtOH-AcOEt	C ₆ H ₃ N ₃ F ₂	68.33	3.23	14.94	F 13.51	
C., H	H		310-311	colorless	EtOH-AcOEt	C ₆ H ₃ N ₃ F ₂	68.63	3.47	14.99	F 13.72	
C., H	H		325(d)	colorless	EtOH	C ₆ H ₃ N ₃ SCl	68.33	3.23	14.94	F 13.51	
C., H	H		>310	colorless	EtOH	C ₆ H ₃ N ₃ SCl	59.74	3.63	13.71	10.61	
C., 7-Cl	H						58.85	2.82	14.71	11.22	
							58.61	3.11	14.40	11.11	

5 10 15 20 25 30 35 40 45 50 55

Table 3 (4)

C.,	7-Cl	H		> 315	colorless	OEtLi-HCOH	C ₁₀ H ₁₁ N ₂ ClF	64.55	3.05	14.11	Cl 11.91
C.,	H	H		205-296	colorless	EtOEt-AcOEt	C ₁₀ H ₁₁ N ₂ S	67.90	4.18	15.84	12.08
C.,	7-Cl	H		217-289	colorless	EtOEt	C ₁₀ H ₁₁ N ₂ SCl	67.84	4.35	15.64	11.87
C.,	7-Cl	H		307-308	colorless	EtOH	C ₁₀ H ₁₁ N ₂ SCl	60.10	3.36	14.20	10.69
C.,	8-F	H		> 310	colorless	EtOEt-AcOEt	C ₁₀ H ₁₁ N ₂ SCl·1/2H ₂ O	59.65	3.42	13.91	10.62
C.,	8-F	H		272-274	colorless	EtOEt-AcOEt	C ₁₀ H ₁₁ N ₂ F ₂	59.78	3.59	14.03	10.20
C.,	7-Me	H		323-326	colorless	EtOEt-AcOEt	C ₁₀ H ₁₁ N ₂ SF	63.59	3.56	14.83	11.32
C.,	7-Me	H		> 315	colorless	EtOEt-AcOEt	C ₁₀ H ₁₁ N ₂ S·1/2H ₂ O	67.33	4.24	15.66	
C.,	7-Cl	H		> 300	colorless	EtOEt-AcOEt	C ₁₀ H ₁₁ N ₂ S	67.18	4.51	15.64	
C.,	7-Cl	8-Cl		303-304.5	colorless	EtOEt-AcOEt	C ₁₀ H ₁₁ N ₂ SCl ₂	68.79	4.69	15.04	
C.,	H	H		254-256	colorless	AcOEt-HCOH	C ₁₀ H ₁₁ N ₂ O·1/2H ₂ O	67.59	4.63	21.02	
C.,	H	H						67.76	4.68	20.74	

5 10 15 20 25 30 35 40 45 50 55

Table 3 (5)

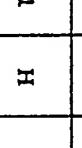
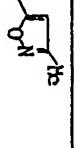
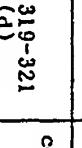
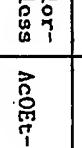
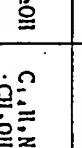
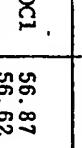
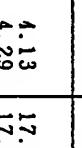
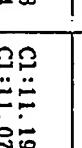
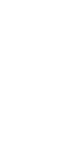
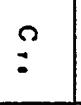
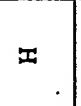
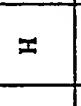
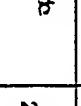
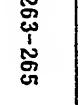
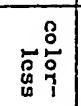
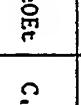
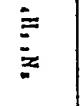
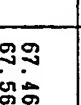
C.,	7-F	H		309-311 (d)	color- less	AcOEt-MeOH	C ₄ H ₄ N ₂ O ₄	63.82 63.58	3.92 4.06	19.84 19.74	
C.,	7-F	H		308-310 (d)	color- less	AcOEt-MeOH	C ₄ H ₄ N ₂ O ₄	62.68 62.46	3.38 3.50	20.88 20.67	
C.,	8-F	H		293-295	color- less	AcOEt	C ₄ H ₄ N ₂ O ₄ 1/H ₂ O	61.87 61.65	3.70 3.51	20.28 20.54	
C.,	7-NO ₂	H		280-282 (d)	color- less	AcOEt-MeOH	C ₄ H ₄ N ₂ O ₄ 1/H ₂ O	63.91 63.69	4.49 4.44	19.23 19.25	
C.,	7-NO ₂	H		303-305 (d)	color- less	AcOEt-MeOH	C ₄ H ₄ N ₂ O ₄ 1/H ₂ O	67.40 67.36	4.65 4.67	20.96 21.02	
C.,	8-Cl	H		310-311 (d)	light yellow	AcOEt-MeOH	C ₄ H ₄ N ₂ O ₄ 1/H ₂ O	55.96 56.08	3.58 3.72	18.64 18.57	
C.,	7-Cl	8-F		322-325 (d)	color- less	AcOEt-MeOH	C ₄ H ₄ N ₂ O ₄ 1/H ₂ O	53.43 53.40	2.99 3.26	17.80 17.68	
C.,	7-Cl	H		319-321 (d)	color- less	AcOEt-MeOH	C ₄ H ₄ N ₂ O ₄ 1/H ₂ O	56.87 56.62	4.13 4.29	17.68 17.54	Cl:1:1.19 Cl:1:1.07
C.,	7-CF ₃	H		295-297 (d)	color- less	AcOEt	C ₄ H ₄ N ₂ O ₄	56.60 56.58	2.85 3.05	17.60 17.61	
C.,	7-Cl	9-Cl		256-258	color- less	EtOH	C ₄ H ₄ N ₂ O ₄	52.68 52.40	2.53 2.62	17.56 17.41	Cl:22.22 Cl:22.42
C.,	6-F	H		275-277 (d)	color- less	AcOEt-EtOH	C ₄ H ₄ N ₂ O ₄	62.68 62.49	3.38 3.63	20.88 20.82	

Table 3 (6)

C ..	H	H		271-274 (d)	color- less	AcOEt	C ₁₁ H ₁₁ N ₀ /H ₂ O	65.47 65.41	3.49 3.74	23.49 23.28
C ..	7-Cl	H		302-306 (d)	color- less	MeOH-CHCl ₁ ,	C ₁₁ H ₁₀ N ₀ OC1 /H ₂ O	57.21 57.20	2.68 2.94	20.53 20.36
C ..	7-F	H		297-299	color- less	AcOEt-MeOH	C ₁₁ H ₁₀ N ₀ OF /H ₂ O	60.70 60.96	2.87 3.17	21.78 21.73
C ..	H	H		273-274	color- less	AcOEt	C ₁₁ H ₁₁ N ₀	67.19 67.23	4.02 4.22	22.38 22.20
C ..	7-F	H		328-330 (d)	color- less	AcOEt-EtOH	C ₁₁ H ₁₀ N ₀ OF	62.68 62.61	3.38 3.58	20.88 20.68
C ..	H	H		268-269	color- less	AcOEt	C ₁₁ H ₁₁ N ₀	68.17 68.16	4.57 4.74	21.19 21.01
C ..	7-F	H		307-310 (d)	color- less	AcOEt-EtOH	C ₁₁ H ₁₀ N ₀ OF	63.82 63.74	3.92 4.08	19.84 19.68
C ..	8-F	H		312-315 (d)	color- less	AcOEt-MeOH	C ₁₁ H ₁₀ N ₀ OF	62.68 62.56	3.38 3.56	20.88 20.66
C ..	7-Cl	H		344-347 (d)	color- less	MeOH	C ₁₁ H ₁₀ N ₀ Cl	59.06 58.78	3.18 3.22	19.67 19.44
C ..	H	H		274-275	color- less	AcOEt-EtOH	C ₁₁ H ₁₀ N ₀ S	62.30 62.56	3.88 4.12	20.76 20.62
C ..	H	H		309-310 (d)	color- less	AcOEt-EtOH	C ₁₁ H ₁₀ N ₀ S	62.43 62.68	3.87 4.15	20.80 20.89

Table 3 (7)

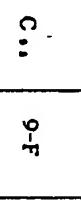
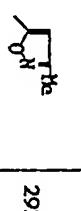
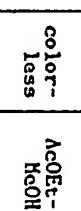
C.,	H	H		296-298	colorless	MeOH	C ₄ H ₈ N ₂ O	57.98 58.18	4.12 3.98	26.01 25.90	
C.,	H	H		290-293 (d)	colorless	MeOH	C ₄ H ₈ N ₂ S .H ₂ O	53.13 53.30	3.34 3.39	25.81 25.54	S:11.81 S:11.69
C.,	H	H		303-305 (d)	colorless	MeOH-AcOEt	C ₄ H ₈ N ₂ S	63.13 63.29	3.78 3.80	21.03 20.83	
C.,	H	H		245-246 (d)	colorless	AcOEt-MeOH	C ₄ H ₈ N ₂ S .H ₂ O	62.61 62.89	3.85 4.00	20.86 20.57	
C.,	H	H		292-294 (d)	colorless	AcOEt-MeOH	C ₄ H ₈ N ₂ S	61.88 61.94	3.19 3.30	22.20 21.97	
C.,	H	H		242-244	colorless	AcOEt	C ₄ H ₈ N ₂ S .H ₂ O	61.02 61.27	3.31 3.57	21.89 21.81	
C.,	H	H		276-278	colorless	EtOH-AcOEt	C ₄ H ₈ N ₂ S .H ₂ O	66.50 66.65	4.54 4.73	27.69 27.47	
C.,	H	H		263-265	colorless	EtOH-AcOEt	C ₄ H ₈ N ₂	67.46 67.56	4.45 4.74	28.09 27.85	
C.,	H	H		251-253	colorless	EtOH-AcOEt	C ₄ H ₈ N ₂ O	67.19 67.29	4.03 4.09	22.39 22.13	
C.,	H	H		242-243	colorless	AcOEt	C ₄ H ₈ N ₂ S .H ₂ O	61.02 61.27	3.31 3.57	21.89 21.81	
C.,	8-Cl	H		299-302 (d)	light yellow	AcOEt-MeOH	C ₄ H ₈ N ₂ CCl	57.68 57.69	2.60 2.76	20.69 20.53	

10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54

Table 3 (8)

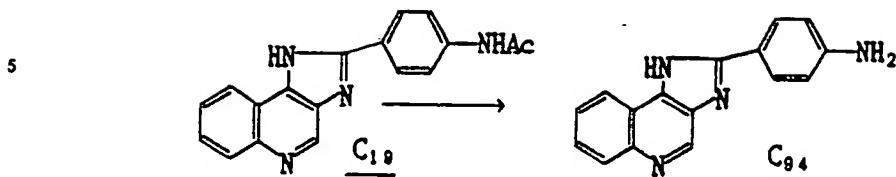
C ..	8-F	H		308-310 (d)	color- less	MeOH-AcOEt	C ₁ ,H,N,O,F	61.41	2.77	22.03	
C ..	8-F	H		308- (d) 310.5	color- less	MeOH-AcOEt	C ₁ ,H,N,O,F	61.41	2.77	22.03	
C ..	8-OH	H		279-281 (d)	color- less	MeOH-AcOEt	C ₁ ,H,N,O, H ₂ O	62.10	3.93	20.69	
C ..	7-F	H		316-319 (d)	color- less	MeOH-AcOEt	C ₁ ,H,N,O, H ₂ O	62.19	3.92	20.69	
C ..	6-F	H		329-332 (d)	color- less	MeOH- CH ₂ Cl,	C ₁ ,H,N,O	60.88	2.85	21.85	
C ..	7-Ha	H		294- (d) 297.5	color- less	AcOEt	C ₁ ,H,N,O	61.41	2.77	22.03	
C ..	7-CF ₃	H		324-328 (d)	color- less	MeOH-AcOEt	C ₁ ,H,N,O,F	61.59	3.02	21.99	
C ..	9-F	H		277-279 (d)	color- less	MeOH-AcOEt	C ₁ ,H,N,O,F	67.19	4.02	22.38	
C ..	9-F	H		282- (d) 284.5	color- less	MeOH-AcOEt	C ₁ ,H,N,FS	55.27	2.31	18.41	
C ..	6-F	H		320-322	color- less	EtOH	C ₁ ,H,N,SF	62.66	3.26	15.69	
C ..	9-Cl	H		210-212	color- less	MeOH	C ₁ ,H,N,OC ₁ , H ₂ O	56.69	2.97	20.03	Cl: 12.37 12.51

Table 3 (9)

C.,	9-Cl	H		243-245	colorless	MeOH	C ₁₁ H ₈ N ₂ SCl	58.84 58.79	2.82 3.02	14.71 14.86	Cl:12.41, S:11.22 Cl:12.30, S:10.96
C.,	9-Cl	H		202-203	colorless	MeOH	C ₁₁ H ₈ N ₂ SCl	60.09 59.88	3.36 3.50	14.02 14.00	Cl:11.83, S:10.70 Cl:11.86 S:10.64
C.,	9-F	H		292-294	colorless	AcOEt-MeOH	C ₁₁ H ₈ N ₂ OF	62.68 62.83	3.38 3.52	20.88 20.84	

Example 94

2-(4-Aminophenyl)-1H-imidazo[4,5-c]quinoline C₂₄



A suspension of 320 mg of 2-(4-acetylaminophenyl)-1H-imidazo[4,5-c]quinoline C₁₉ in 10 ml of 1N sodium hydroxide is refluxed for 1.5 hours. After the mixture is cooled and neutralized with acetic acid, the resulting white crystals are filtered, washed successively with water and ethanol, and dried to give 195 mg -
 15 (71%) of C₉₄.
 m.p. ca. 340°C (from ethanol)
 Anal. Calcd. (%) (for C₁₂H₁₂N₂•1/8C₂H₅OH)
 : C, 73.36; H, 4.83; N, 21.06.
 Found (%) : C, 73.44; H, 4.93; N, 20.95.

20

Example 95

2-(4-methylphenyl)-1H-imidazo[4,5-c]quinoline C₉₅

25

A suspension of 326 mg of 4-methylbenzoic acid and 318 mg of 3,4-diaminoquinoline A₁ in 10 g of polyphosphoric acid is heated with stirring at 180°C for 4 hours. The cooled mixture is poured into ice-water and neutralized with aqueous sodium hydroxide. The resulting solid is chromatographed on silica gel with chloroform -methanol (25:1 v/v) as eluent to give 430 mg (83%) of C₉₅ as white crystals.
 30 m.p.: 326 -329°C (dec.) (from ethanol)
 Anal. Calcd. (%) (for C₁₂H₁₂N₂• 1/3H₂O)
 : C, 76.96; H, 5.19; N, 15.84.
 Found (%) : c, 76.86; H, 4.84; N, 15.52.

35

Example 96

2-(4-Chlorophenyl)-1H-imidazo[4,5-c]quinoline C₉₆

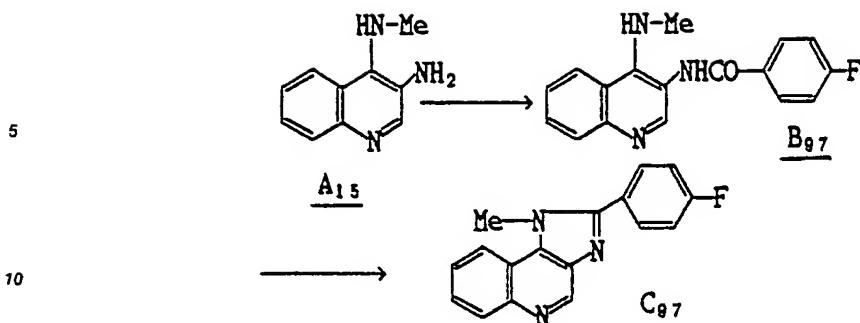
40

A suspension of 239 mg of 4-chlorobenzoic acid and 470 mg of 3,4-diaminoquinoline A₁ in 9 g of polyphosphoric acid is heated at 185°C for 4 hours with stirring under nitrogen. The same work-up as described in Example 95 gives 248 g (59%) of C₉₆ as white crystals.
 m.p. 335 -337°C (dec.) (from ethanol)
 Anal. Calcd. (%) (for C₁₂H₁₂N₂Cl)
 : C, 68.70; H, 3.60; N, 15.02; Cl, 12.68.
 Found (%) : C, 68.42; H, 3.71; N, 14.83; Cl, 12.76.

50

Example 97
2-(4-Fluorophenyl)-1-methyl-1H-imidazo[4,5-c]quinoline C₉₇

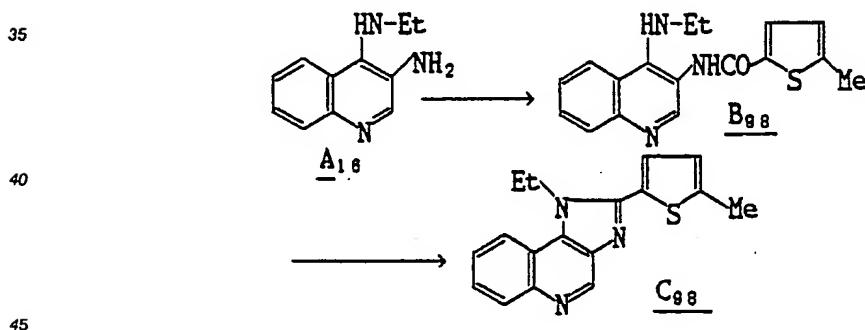
55



To a solution of 390 mg of 4-fluorobenzoic acid in 6 ml of anhydrous hexamethylphosphoramide and 0.6 ml of anhydrous acetonitrile is added dropwise 320 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring at the same temperature for 30 minutes, a solution of 440 mg of 3-amino-4-methylaminoquinoline A₁₅ in 4 ml of anhydrous hexamethylphosphoramide is added and stirred at 0°C for 2.5 hours. The same work-up as described in Example 1 gives 750 kg of B₉₇ as a white solid. It is dissolved in 10 ml of acetic acid and refluxed for 1 hour. The mixture is concentrated under reduced pressure and the residue is shaken with ethyl acetate -saturated aqueous sodium bicarbonate. The organic layer is separated, washed successively with water and aqueous sodium chloride, and dried. The solvent is evaporated and the residue is crystallized from n-hexane to give 610 mg (87%) of C₉₇ as white crystals.
m.p. : 185 -187°C (from ethyl acetate)
Anal. Calcd. (%) (for C₁₁H₁₂N₂F)
: C, 73.63; H, 4.36; N, 15.15; F, 6.85.
Found (%) : C, 73.73; H, 4.36; N, 15.15; F, 6.77.

Example 98

30 1-Ethyl-2-(5-methylthien-2-yl)-1H-imidazo[4,5-c]quinoline C₉₈



To a solution of 270 mg of 5-methylthiophene-2-carboxylic acid in 5 ml of anhydrous hexamethylphosphoramide and 0.5 ml of anhydrous acetonitrile is added dropwise 215 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring at the same temperature for 30 minutes, a solution of 320 mg of 3-amino-4-ethylaminoquinoline A₁₆ in 0.5 ml of anhydrous hexamethylphosphoramide is added and stirred at 0 -5°C for 3 hours. The same work-up as described in Example 1 gives 510 mg of B₉₈ as a white solid. It is suspended in 10 ml of acetic acid and refluxed for 1 hour. The mixture is concentrated and the residue is shaken with ethyl acetate-saturated aqueous sodium bicarbonate. The organic layer is separated, washed successively with water and saturated aqueous sodium chloride, and dried. The solvent is evaporated and the residue is chromatographed on silica gel with chloroform -methanol (20:1 v/v) as eluent to give 380 mg - (76%) of C₉₈ as colorless crystals.
m.p.: 205 -206°C (dec.) (from ethyl acetate)

Anal. Calcd. (%) for C₁₄H₁₀N₂S
 : C, 69.60; H, 5.15; N, 14.32; S, 10.93.
 Found (%) : C, 69.66; H, 4.96; N, 14.30; S, 10.88.

5

Example 99

2-(4-Methyloxazol-5-yl)-1H-imidazo[4,5-c]quinoline C₁₀

10 To a solution of 300 mg of 4-methyloxazole-5-carboxylic acid in 4 ml of hexamethylphosphoramide and 0.4 ml of acetonitrile is added 268 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring at the same temperature for 30 minutes, 340 mg of 3,4-diaminoquinoline A₁ is added and stirred at 0 -5°C for 3 hours. The mixture is diluted with ice-water and neutralized with saturated aqueous sodium bicarbonate. The resulting solid is filtered and washed with water to give 425 mg of 4-amino-3-(4-methyloxazole-5-ylcarbonylamino)quinoline as crude crystals. It is suspended in 12 ml of Dowtherm A (Dow Chemical Co.) and refluxed for 2.5 hours. The cooled mixture is diluted with 50 ml of n-hexane and the resulting solid is collected by filtration. It is chromatographed on silica gel with dichloromethane -methanol (20:1 v/v) as eluent to yield a crude solid which is recrystallized from ethyl acetate -methanol, giving 297 mg of C₁₀ as pale yellow crystals.

15 m.p. 289 -292°C (dec.)

Anal. Calcd. (%) (for C₁₄H₁₀N₂O•1/8H₂O)
 : C, 66.59; H, 4.09; N, 22.19.
 Found (%) : C, 66.86; H, 4.18; N, 21.98.

25

Example 100

2-(3-Methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline hydrochloride C₁₀·HCl

30 To an ethanolic solution of 300 mg of 2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline C₁₀ is added ethanolic hydrogen chloride at room temperature. The mixture is evaporated and the residue is washed with acetone to give C₁₀·HCl as crystals melting at 248.5 -252°C (dec.).

Anal. Calcd. (%) (for C₁₄H₁₀N₂OCl•1/3H₂O)
 : C, 57.45; H, 4.02; N, 19.14; Cl, 12.11

35 Found (%) : C, 57.64; H, 4.27; N, 18.90; Cl, 12.23

Example 101

40 3-Methanesulfonyl-2-(3-methylisoxazol-5-yl)-3H-imidazo[4,5-c]quinoline C₁₁

To a solution of 300 mg of 2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline C₁₀ in 20 ml of tetrahydrofuran is added 50 mg of 60% sodium hydride in mineral oil and stirred at 75°C for 2 hours under nitrogen. To the cooled mixture is added dropwise 180 mg of methanesulfonyl chloride and stirred at 0 - 45 5°C for 2 hours. The mixture is concentrated under reduced pressure and the residue is poured into ice-water. The resulting solid is collected by filtration and chromatographed on silica gel with dichloromethane - methanol (50:1 v/v) as eluent, yielding 159 mg (40%) of C₁₁ as white crystals.

m.p. 167.5 -169°C (dec.) (from ethyl acetate)

Anal. Calcd. (%) (for C₁₅H₁₂N₂O₃S)
 : C, 54.86; N, 3.68; N, 17.06
 Found (%) : C, 54.95; H, 3.97; N, 16.79

55

Example 102

1-Methyl-2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline C₁₀₂

5 To a solution of 245 mg of 3-methylisoxazole-5-carboxylic acid in 20 ml of hexamethylphosphoramide and 0.4 ml of acetonitrile is added 226 mg of thionyl chloride at -5 -0°C. After stirring at the same temperature for 30 minutes, 330 mg of 3-amino-4-methylaminoquinoline A₁₅ is added and stirred at 0 - 5°C for 5 hours. The mixture is diluted with 50 ml of ice-water and neutralized with saturated aqueous sodium bicarbonate. The resulting solid is filtered and washed with water to give 361 mg (67%) of 4-methylamino-3-[3-methylisoxazole-5-ylcarbonyl]aminoquinoline. It is suspended in 4 ml of hexamethylphosphoramide and 1 ml of acetic acid and stirred at 180°C (bath temperature) for 40 minutes. The cooled mixture is poured into ice-water and neutralized with aqueous sodium bicarbonate. The resulting solid is filtered, washed with water and chromatographed on silica gel with dichloromethane -methanol (25:1 v/v) as eluent. The product obtained is recrystallized from dichloromethane -methanol to give 294 mg of C₁₀₂ as white crystals melting at 281 -284°C (dec).

10 Anal. Calcd. (%) (for C₁₅H₁₂N₄O) : C, 68.17; H, 4.57; N, 21.19.

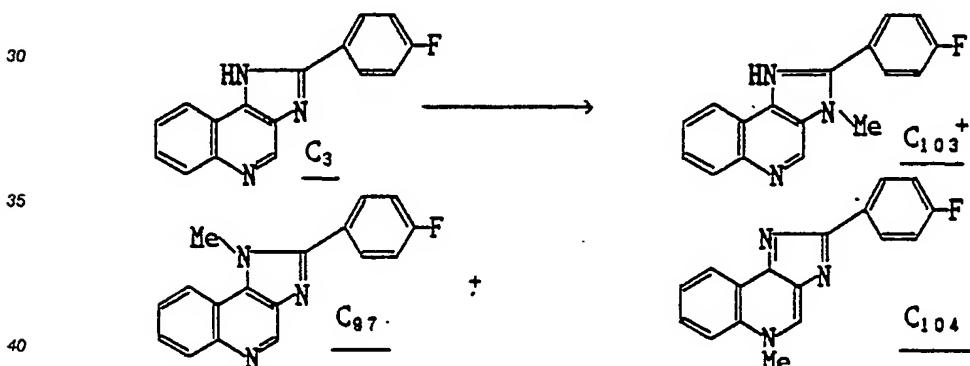
15 Found (%) : C, 68.29; N, 4.57; N, 21.21.

20 NMR (CDCl₃-CD₃OD): δ 2.46(s,3H), 4.57(s,3H), 6.99(s,1H), 7.6-8.7(m,4H), 9.23(s,1H).

20

Example 103

25 2-(4-Fluorophenyl)-3-methyl-3H-imidazo[4,5-c]quinoline C₁₀₃, 2-(4-Fluorophenyl)-1-methyl-1H-imidazo[4,5-c]-
25 quinoline C₉₇, and 2-(4-Fluorophenyl)-5-methyl-5H-imidazo[4,5-c]quinoline C₁₀₄



30 To a solution of sodium ethoxide (prepared from 70 mg of metallic sodium and 10 ml of anhydrous ethanol) is added 520 mg of 2-(4-fluorophenyl)-1H-imidazo[4,5-c]quinoline C₁ at room temperature under nitrogen and stirred for 5 minutes. To the mixture is added 0.5 ml of methyl iodide and stirred at 50°C for 1 hour. The mixture is poured into ice-water and extracted with ethyl acetate. The extract is washed with water and dried. Evaporation of the solvent gives a residue which is chromatographed on silica gel with chloroform -methanol (30:1 v/v) as eluent. The fractions containing the compound with an Rf=0.35 are combined and evaporated to give 90 mg (16%) of 3-methyl derivative C₁₀₂ as colorless crystals.

35 m.p 168 -170°C (ethyl acetate -n-hexane)

Anal. Calcd. (%) (for C₁₅H₁₂N₃F) :

: C, 73.63; H, 4.36; N, 15.15; F, 6.85.

35 Found (%) : C, 73.86; H, 4.56; N, 15.13; F, 6.86.

40 NMR (CDCl₃) : δ 4.02(s,2H), 7.17-8.77(m,8H), 9.10(s,1H)

45 Then evaporation of the combined fractions containing the product with an Rf=0.27 yields 60 mg - (11%) of 1-methyl derivative C₁₀₂ which is identical with the compound obtained in Example 97.

Lastly the combined fractions containing the compound with an $R_f = 0.12$ is evaporated to give 340 mg - (62%) of 5-methyl derivative C_{104} as colorless crystals.

m.p. 277 -278°C (from ethyl acetate -methanol)

Anal. Calcd. (%) (for $C_{10}H_{11}N_2F$)

5 : C, 73.63; N, 4.36; N, 15.15; F, 6.85.

Found (%) : C, 73.64; H, 4.36; N, 15.05; F, 6.76.

NMR ($CDCl_3$): δ 4.23(s,3H), 7.03-8.93(m,8H), 8.56(s,1H).

10 Example 104

3-Methyl-2-(3-methylisoxazol-5-yl)-3H-imidazo[4,5-c]quinoline C_{105} , 1-Methyl-2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline C_{106} and 5-Methyl-2-(3-methylisoxazol-5-yl)-5H-imidazo[4,5-c]quinoline C_{107}

15 To a solution of 450 mg of 2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline C_{104} in 39 ml of tetrahydrofuran is added 80 mg of 60% sodium hydride in mineral oil and stirred at 60°C for 1.5 hours under nitrogen. To the cooled mixture is added dropwise 385 mg of methyl iodide in 2 ml of tetrahydrofuran at 0 -5°C. After stirring at 0 -5°C for 30 minutes and then at 40°C for 4 hours, the mixture is evaporated and the residue is chromatographed on silica gel with dichloromethane -methanol (50:1 v/v) as eluent, to give 58 mg (12%) of 3-methyl derivative C_{105} as white crystals.

m.p. 179.5 - 182°C (from ethyl acetate)

Anal. Calcd. (%) (for $C_{11}H_{12}N_2 \bullet 1/4H_2O$)

: C, 67.03; H, 4.69; N, 20.84.

Found (%) : C, 67.16; N, 4.98; N, 20.62.

25 NMR ($CDCl_3$ - CD_3OD): δ 2.46(s,3H), 4.35(s,3H), 7.13(s,1H), 7.6 -8.7 (m,4H), 9.13 (s,1H).

The further elution with the same solvent yields 42 mg (9%) of 1-methyl derivative C_{106} which is identical with the compound described in Example 102.

Then the eluate with dichloromethane -methanol (25:1 v/v) affords 322 mg (68%) of 5-methyl derivative C_{107} as white crystals.

30 m.p.: 308 -309°C (dec.) (from ethyl acetate -methanol)

Anal. Calcd. (%) (for $C_{11}H_{12}N_2O$)

: C, 68.17; H, 4.57; N, 21.19.

Found (%) : C, 68.14; H, 4.76; N, 21.12.

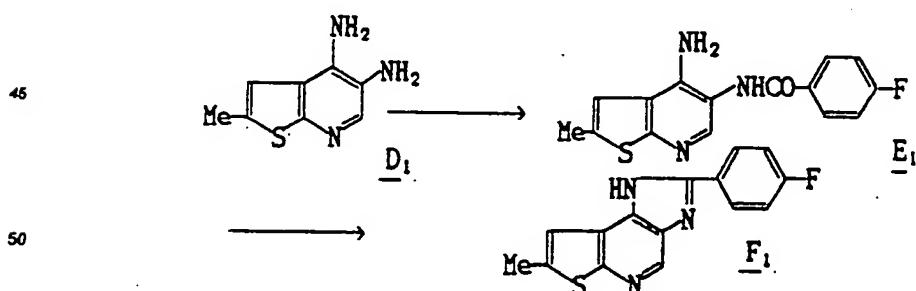
NMR ($CDCl_3$ - CD_3OD): δ 2.42(s,3H), 4.40(s,3H), 6.99(s,1H), 7.6-8.9 (m,4H), 9.07(s,1H).

35

Example 105

2-(4-Fluorophenyl)-7-methyl-1H-imidazo[4,5-c]thieno[2,3-b]pyridine F ,

40

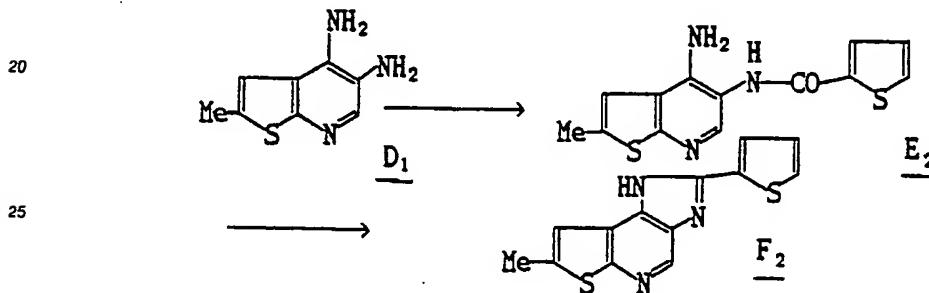


45 To a solution of 308 mg of 4-fluorobenzoic acid in 5 ml of anhydrous hexamethylphosphoramide and 0.5 ml of anhydrous acetonitrile is added dropwise 250 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring at the same temperature for 30 minutes, 358 mg of diaminothienopyridine D_1 is added and stirred at 0 -5°C for 3 hours. The mixture is diluted with ice-water and neutralized with saturated aqueous

sodium bicarbonate. The resulting crystals are filtered, washed with water and dried to yield 630mg of 4-amino-2-methyl-5-(4-fluorobenzoylamino)thieno[2,3-b]pyridine E. It is suspended in 15 ml of polyphosphoric acid and heated at 140°C with stirring under nitrogen. The cooled mixture is poured into ice-water and neutralized with aqueous sodium hydroxide. The product is extracted with ethyl acetate and the extract is washed with water, dried and evaporated. The residue is chromatographed on silica gel with chloroform-methanol (25:1 v/v) as eluent to afford 457 mg (81%) of E as colorless crystals.
 5 m.p.: 313 -316°C (from ethanol)
 Anal.Calcd. (%) (for C₁₅H₁₄N₂S)
 : C, 63.58; H, 3.55; N, 14.83; S, 11.31.
 10 Found (%) : C, 63.32; H, 3.79; N, 14.61; S, 11.09.

Example 106

15 2-(Thien-2-yl)-7-methyl-1H-imidazo[4,5-d]thieno[2,3-b]pyridine F,



20 To a solution of 212 mg of thiophene-2-carboxylic acid in 4 ml hexamethylphosphoramide and 0.4 ml of acetonitrile is added dropwise 188 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring at 0 -5°C for 30 minutes, 269 mg of diaminothienopyridine D₁ is added and stirred at 0 -5 °C for 3 hours. The same work-up as described in Example 105 gives 403 mg of E₂ as crude crystals. It is suspended in 20 ml of Dowtherm A (Dow Chemical Co.) and refluxed for 3 hours under nitrogen. The cooled mixture is diluted with n-hexane and the resulting crystals are filtered. It is chromatographed on silica gel with chloroform - methanol (25:1 v/v) as eluent to give 286 mg (70%) of F₂ as colorless crystals.
 25 m.p. : 284 -287°C (from methanol -ethyl acetate)
 Anal. Calcd. (%) (for C₁₃H₁₂N₂S)
 : C, 57.54; H, 3.34; N, 15.48; S, 23.68.
 30 Found (%) : C, 57.46; H, 3.60; N, 15.39; S, 23.67.

Example 107-114

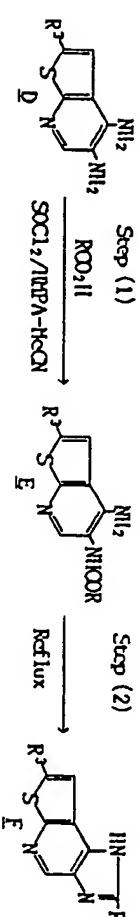
35 According to the method illustrated by Example 106, Compounds F₁-F₁₀ are obtained under the conditions shown in Table 4. Table 5 shows the physical properties of these compounds.

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Table 4



Ex. No.	R ^a R	Step (1)					Step (2)			Compound F	
		RCO, II (mg)	SOCl ₂ , HMPA - MeCN (mL)	Yield of D (mL)	React- ion time (hrs.)	Compound E (mg)	Yield of E (mg)	Boethmer A ion time (hrs.)	React- ion time (hrs.)	Yields (mg)	Compd. No.
107	Me	213	190	4 - 0.4	270	4	390	370	7.4	2	310
108	Me	199	160	4 - 0.4	230	4	375	350	7	3	310
109	Me	199	160	4 - 0.4	230	4	372	350	7	3.5	305
110	Me	199	160	4 - 0.4	230	4	355	330	6.6	16	250
111	H	214	191	4 - 0.4	250	3.5	387	370	7.4	2	315
112	H	214	191	4 - 0.4	250	3.5	378	350	7	2	300
113	H	215	174	4 - 0.4	230	3.5	300	280	5.6	2	240
114	Me	229	230	4 - 0.4	330	5	514	510	10	1	362

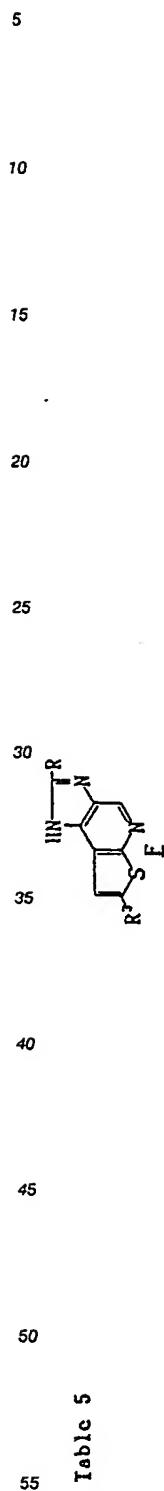


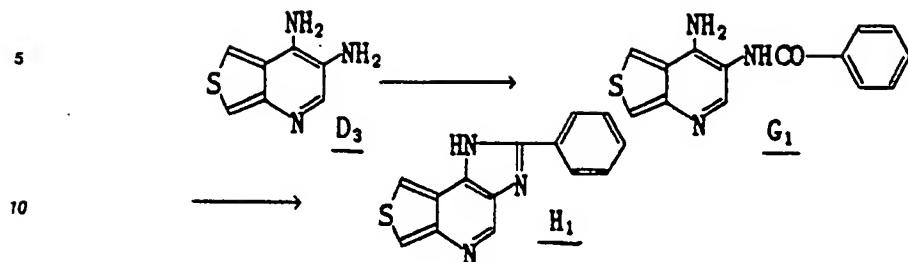
Table 5

Compd. No.	R ^a	R	m.p. (°C)	Appea- rance	Solvent for crystalln.	Molecular Formula	Elementary Analysis Up (Calcd.). Down (Found)		
							C	H	N
F ₁	He		295-296	color- less	AcOEt	C ₁₁ H ₁₁ N ₂ S ₂	57.54	3.34	15.48
F ₂	He		277-278	color- less	EtOAc	C ₁₁ H ₁₁ N ₂ S ₂ 1/2H ₂ O	57.44	3.61	15.46
F ₃	He		268-270	color- less	EtOAc	C ₁₁ H ₁₁ N ₂ S ₂	58.46	3.94	14.61
F ₄	He		263-266	color- less	EtOAc	C ₁₁ H ₁₁ N ₂ S ₂	58.49	4.12	14.56
F ₅	H		290-293	color- less	AcOEt-n-hexane	C ₁₁ H ₁₁ N ₂ S ₂ 1/2H ₂ O	58.92	3.88	14.72
F ₆	H		277-279	color- less	AcOEt-n-hexane	C ₁₁ H ₁₁ N ₂ S ₂ 1/2AcOEt	54.72	3.41	14.73
F ₇	H		307-310	color- less	AcOEt	C ₁₁ H ₁₁ N ₂ S ₂ 1/2AcOEt	55.60	3.23	15.59
F ₈	He		297-299	color- less	AcOEt-MeOH	C ₁₁ H ₁₁ N ₂ S ₂	56.23	3.14	21.86

-46-

Example 115

2-Phenyl-1H-imidazo[4,5-d]thieno[3,4-b]pyridine H,



To a solution of 189 mg of benzoic acid in 5 ml of anhydrous hexamethylphosphoramide and 0.5 ml of anhydrous acetonitrile is added dropwise 174 mg of thionyl chloride at 0°C under nitrogen. After stirring at 0°C for 30 minutes, 239 mg of diaminothienopyridine D₃ is added and stirred for 3 hours. The mixture is diluted with ice-water and neutralized with aqueous sodium bicarbonate. The resulting crystals are filtered, washed with water and dried to give 280 mg of G₁. It is suspended in 4.2 ml of hexamethylphosphoramide and 1.1 ml of acetic acid, and heated at 170°C for 30 minutes. The cooled mixture is diluted with ice-water and extracted with ethyl acetate, and the extract is washed with water and dried. After the solvent is evaporated, the residue is chromatographed on silica gel with chloroform -methanol (50:2 v/v) to give 170 mg (51%) of H₁ as colorless crystals.
 m.p. 308 -312°C (dec.) (from ethyl acetate -methanol)
 Anal. Calcd. (%) (for C₁₁H₁₀N₂S•1/3H₂O)
 : C, 65.35; H, 3.79; N, 16.33.
 Found (%) : C, 65.29; H, 3.73; N, 16.13.

Example 116

2-(4-Fluorophenyl)-1H-imidazo[4,5-d]thieno[3,4-b]pyridine H₂,

According to the method illustrated by Example 115, 240 mg (50%) of H₂ is obtained from 281 mg of 4-fluorobenzoic acid and 300 mg of diaminothienopyridine D₃.
 m.p. : 302 -305°C (from methanol -ethyl acetate)
 Anal. Calcd. (%) (for C₁₁H₁₀N₂F)
 : C, 62.44; H, 2.99; N, 15.60.
 Found (%) : C, 62.23; H, 3.26; N, 15.28.

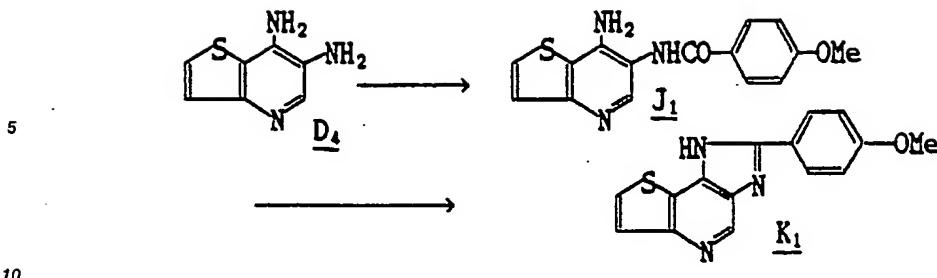
Example 117

2-(5-Chlorothien-2-yl)-1H-imidazo[4,5-d]thieno[3,4-b]pyridine H₃,

According to the method illustrated by Example 115, 259 mg of H₃ is obtained from 325 mg of 5-chlorothiophene-2-carboxylic acid and 300 mg of diaminothienopyridine D₃.
 m.p. : 301 -304°C (dec.)
 Anal. Calcd. (%) (for C₁₁H₁₀N₂ClS)
 : C, 49.39; H, 2.07; N, 14.40.
 Found (%) : C, 49.09; H, 2.17; N, 14.16.

Example 118

2-(4-Methoxyphenyl)-1H-imidazo[4,5-d]thieno[3,2-b]pyridine K,



To a solution of 233 mg of 4-methoxybenzoic acid in 4 ml of hexamethylphosphoramide and 0.4 ml of acetonitrile is added 174 mg of thionyl chloride at 0°C under nitrogen. After stirring at 0°C for 30 minutes, 230 mg of diaminothienopyridine D₄ is added and stirred at 0°C for 4 hours. The mixture is diluted with ice-water and neutralized with aqueous sodium bicarbonate. The resulting crystals are filtered, washed with water and dried to yield 348 mg (84%) of J₁. The mixture of J₁ and 6.6 ml of Dowtherm A (Dow Chemical Co.) is refluxed for 2 hours. The cooled mixture is diluted with n-hexane and allowed to stand to give 300 mg (95%) of K₁ as colorless crystals.
 m.p. : 285 -287°C (from ethyl acetate -methanol)
 Anal. Calcd. (%) (for C₁₅H₁₄N₂O₂) : C, 63.48; H, 4.25; N, 14.06.
 Found (%) : C, 63.20; H, 4.38, N, 13.86.

25 Example 119 -123

According to the method illustrated by Example 118, Compounds K₂-K₆ are prepared under the conditions shown in Table 6. Table 7 shows the physical properties of these compounds.

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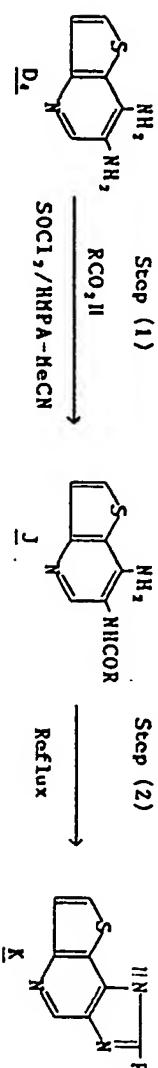
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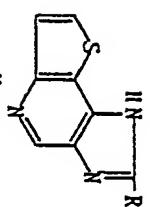
Table 6



Example No.	R	Step (1)					Compound J	Step (2)			Compound K
		RCO, II (mg)	SOCl ₂ (mg)	HMPA - MeCN (ml)	Yield of D ₄ (mg)	React-ion time (hr.)		Yield of J (mg)	React-time (hr.)	Yield (mg)	
119		239	174	4 - 0.4	230	4.0	365	350	7	1.5	320
120		308	250	6 - 0.6	330	3.0	475	400	8	1.5	347
121		268	250	6.6 - 0.7	330	3.0	458	440	9	1.5	373
122		282	250	6 - 0.6	330	3.5	510	500	10	2	438
123		260	181	4 - 0.4	240	3.5	373	350	7	2	310

5 10 15 20 25 30 35 40 45 50 55

Table 7



Compound No.	R	m.p. (°C)	Appar- rance	Solvent for crystalln.	Molecular Formula	Elementary Analysis (%) Up (Calcd.). Down (Found)		
						C	H	N
K ₁		334-337	color- less	MeOH-AcOEt	C ₁₁ H ₈ N, C ₁₁ S·4H ₂ O	57.93	2.95	14.48
						58.11	3.20	14.35
K ₂		275-278	color- less	AcOEt	C ₁₁ H ₈ N, SF·4H ₂ O	61.41	3.13	15.35
						61.70	3.41	14.99
K ₃		288-293	color- less	MeOH-AcOEt	C ₁₁ H ₈ N, S	66.91	3.60	16.72
						66.66	3.86	16.59
K ₄		281-285	color- less	MeOH-AcOEt	C ₁₁ H ₈ N, C ₁₁ S·4H ₂ O	55.36	2.84	16.14
						55.51	3.03	15.86
K ₅		224-228	color- less	MeOH-AcOEt	C ₁₁ H ₈ N, C ₁₁ S·4CH ₂ OH	49.07	2.35	14.01
						49.03	2.64	14.06

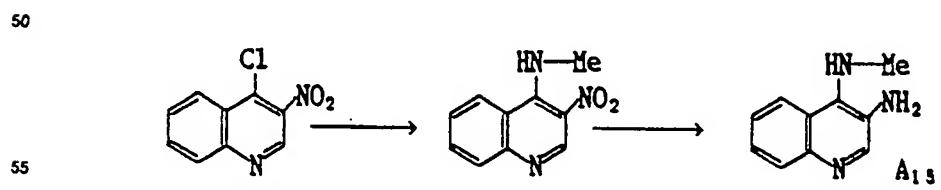
10 15 20 25 30 35 40 45 50 55

3,4-Diaminoquinolines

The starting 3,4-diaminoquinolines are prepared by sequential chlorination, amination and reduction of 3-nitro-4-hydroxyquinolines according to the literature [G. B. Bachman et al., *J. Am. Chem. Soc.*, 69, 365 - 5 (1947) and A. R. Surrey et al., *J. Am. Chem. Soc.*, 73, 2413 (1951)].
The following table shows their melting points.

	Comp. No.	R ₁	R ₂	mp (°C)
10	A ₁	H	H	168 - 170 (dec.)
15	A ₂	6-Cl	H	206 - 209 (dec.)
20	A ₃	7-Cl	H	193 - 195 (dec.)
25	A ₄	6-F	H	196 - 198 (dec.)
30	A ₅	7-Me	H	155 - 158
35	A ₆	6-Cl	7-Cl	250 - 253 (dec.)
40	A ₇	7-F	H	185 - 188 (dec.)
45	A ₈	7-MeO	H	136 - 139 (dec.)
50	A ₉	7-CF ₃	H	179 - 181 (dec.)
55	A ₁₀	6-F	7-Cl	249 - 252 (dec.)
60	A ₁₁	5-Cl	7-Cl	200 - 203 (dec.)
65	A ₁₂	5-Cl	H	157 - 159
70	A ₁₃	8-F	H	167 - 169 (dec.)
75	A ₁₄	5-F	H	168 - 169.5 (dec.)

Referential Example 1

3-Amino-4-methylaminoquinoline A₁₅

To a suspension of 2.0 g of 4-chloro-3-nitroquinoline in 20 ml of dry ethanol is added 15 ml of 30% methylamine in ethanol. The mixture is stirred at room temperature for 30 minutes and concentrated in vacuo. The residue is triturated with excess water. The resulting crystals are collected by filtration and washed repeatedly with water. The crystals are dried over phosphorus pentoxide in vacuo to afford 1.82 g - 5 (93%) of 4-methylamino-3-nitroquinoline.

An analytical sample is recrystallized from ethyl acetate to give yellow crystals melting at 172 -173°C.

Anal. Calcd. (%) (for C₁₀H₁₁N₂O₂)

: C, 59.11; H, 4.46; N, 20.68.

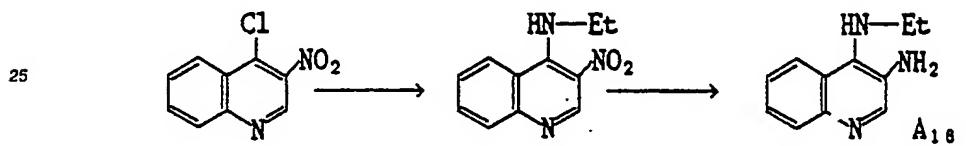
Found (%) : C, 59.33; H, 4.59; N, 20.57.

10 A suspension of 1.7 g of 4-methylamino-3-nitroquinoline in 75 ml of ethanol is hydrogenated in the presence of 300 mg of 10% palladium on carbon at atmospheric pressure. After hydrogen absorption is complete, the catalyst is removed by filtration and the filtrate is concentrated in vacuo. The residue is purified by column chromatography on silica gel. Elution with chloroform -methanol (2:1 v/v) affords 600 mg (41%) of 3-amino-4-methylaminoquinoline A₁₅ as an oil.

15 NMR (CD₃OD) : δ3.05(s,3H), 7.17-7.50(m,2H), 7.60-8.15(m,2H), 8.38 (s,1H).

Referential Example 2

20 3-Amino-4-ethylaminoquinoline A₁₆



30

To a stirred suspension of 1.40 g of 4-chloro-3-nitroquinoline in 30 ml of dry ethanol is introduced excess amount of gaseous ethylamine at room temperature for 3 hours. Treatment of the reaction mixture as in Example 98 yielded 1.41 g (97%) of 4-ethylamino-3-nitroquinoline. Recrystallization from ethyl acetate -n-hexane affords yellow crystals melting at 151 -152°C.

35 Anal. Calcd. (%) (for C₁₁H₁₃N₂O₂)

: C, 60.82; H, 5.10; N, 19.34.

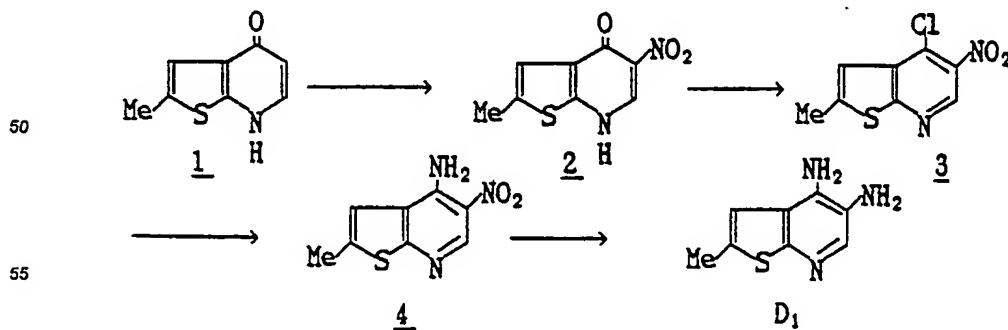
Found (%) : C, 60.93; H, 5.07; N, 19.27.

40 A suspension of 1.34 g of 4-ethylamino-3-nitroquinoline in 40 ml of ethanol is hydrogenated in the presence of 10% palladium on carbon according to the procedure of Referential Example 1, followed by purification to give 0.95 g (82%) of 3-amino-4-ethylaminoquinoline A₁₆ as an oil.

NMR (CD₃OD): δ1.24(t,3H), 3.35(q,2H), 7.33 -7.63(m,2H), 7.77 -8.03(m,2H), 8.30(s,1H).

Referential Example 3

45



(1) 5-Nitro-2-methylthieno[2,3-b]pyridin-4(7H)-one 2

To a solution of 1.65 g of 2-methylthieno[2,3-b]pyridin-4(7H)-one 1 in 45 ml of acetic acid is added dropwise a solution of 1.24 g of concentrated nitric acid ($d = 1.38$) in 5 ml of acetic acid at 110°C. The mixture is heated with stirring at the same temperature for 10 minutes and left on cooling. The resulting crystals are collected by filtration and washed with ethyl acetate to give 1.07 g (51%) of Compound 2 as pale yellow crystals melting at 280 -282°C(dec.).
 Anal. Calcd. (%) (for $C_8H_8N_2O_2S$)
 : C, 45.71; H, 2.87; N, 13.32; S, 15.25.
 Found (%) : C, 45.64; H, 3.42; N, 13.20; S, 15.20.

(2) 4-Chloro-5-nitro-2-methylthieno[2,3-b]pyridine 3

A mixture of 2.26 g of 5-nitro-2-methylthieno[2,3-b]pyridin-4(7H)-one 2 and 10 ml of phosphorus oxychloride is refluxed for 1 hour. The reaction mixture is concentrated to dryness in vacuo and the residue is taken up in the ethyl acetate. The organic phase is dried over magnesium sulfate and treated with activated charcoal. The mixture is filtered and the solvent is evaporated in vacuo. The crude product is recrystallized from ethyl acetate -n-hexane to give 1.90 g (68%) of Compound 3 as colorless melting at 96-98°C.
 Anal. Calcd. (%) (for $C_8H_8N_2O_2SCl$)
 C, 42.02; H, 2.20; N, 12.25; S, 14.02.
 Found (%) : C, 41.92; H, 2.48; N, 12.16; S, 14.12.

25

(3) 4-Amino-5-nitro-2-methylthieno[2,3-b]pyridine 4

To a stirred solution of 1.60 g of 4-chloro-5-nitro-2-methylthieno[2,3-b]pyridine 3 in 50 ml of 2-propanol is introduced excess amount of anhydrous ammonia at 55°C during 3 hours. The reaction mixture is concentrated in vacuo. The residue is washed with ether and suspended in 7 ml of 1N sodium hydroxide solution with stirring. The resulting crystals are collected by filtration and washed with water and a small amount of ethanol to yield 1.37 g (93%) of Compound 4 as orange crystals melting at 238 -240°C.
 Anal. Calcd. (%) (for $C_8H_8N_2O_2S$)
 : C, 45.92; H, 3.37; N, 20.08; S, 15.32.
 Found (%) : C, 45.71; H, 3.40; N, 19.84; S, 15.44.

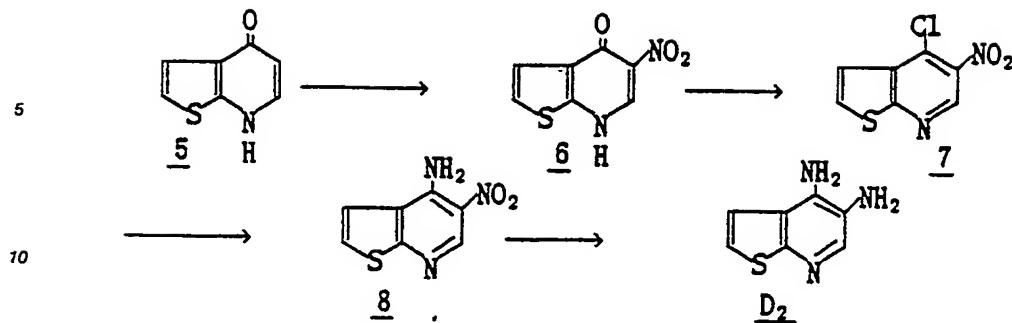
(4) 4,5-Diamino-2-methylthieno[2,3-b]pyridine D,

40

A suspension of 1.25 g of 4-amino-5-nitro-2-methylthieno[2,3-b]pyridine is hydrogenated under atmospheric pressure at room temperature in the presence of 360 mg of 10% palladium carbon for 2 hours. After removal of catalyst, the filtrate is concentrated and the residue is triturated with chloroform to give 866 mg (81%) of Compound D as colorless crystals melting at 204 -209°C.
 Anal. Calcd. (%) (for $C_8H_{10}N_4S$)
 : C, 53.60; H, 5.06; N, 23.44; S, 17.88.
 Found (%) : C, 53.56; H, 5.11; N, 23.24; S, 18.01.

50 Referential Example 4

55



(1) 5-Nitrothieno[2,3-b]pyridin-4(7H)-one 6

To a solution of 3.4 g of thieno[2,3-b]pyridin-4(7H)-one 5 in 105 ml of propionic acid is added 2.79 g of concentrated nitric acid ($d = 1.38$) at 100°C, and then the mixture is stirred at 130°C (bath temperature) for 1 hour. After cooling the reaction mixture, the resulting precipitate is collected by filtration and washed successively with water, methanol and acetone to afford 3.4 g (77%) of Compound 6 as pale yellow crystals melting at 288 - 291°C.

(2) 4-Chloro-5-nitrothieno[2,3-b]pyridine 7

A mixture of 3.4 g of 5-nitrothieno[2,3-b]pyridin-4(7H)-one 6 and 34 ml of phosphorus oxychloride is heated at 115°C (bath temperature) for 1 hour and evaporated to dryness *in vacuo*. The residue is taken up in chloroform and washed with water. The organic phase is dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by column chromatography on silica gel. Elution with dichloromethane - ether (50:1 v/v) affords 3.51 g (94%) of Compound 7 as crystals melting at 110 -113°C.

(3) 4-Amino-5-nitrothieno[2,3-b]pyridine 8

To a stirred suspension of 3.35 g of 4-chloro-5-nitrothieno[2,3-b]pyridine 7 in 160 ml of 2-propanol is introduced excess amount of anhydrous ammonia at 45 -50°C during 4 hours. After removal of the solvent, the residue is suspended in water. The solid is washed with water and cold ether, affording 2.65 g (87%) of Compound 8 as crystals. Recrystallization from methanol -ether gives a pure sample melting at 227 - 228.5°C.

(4) 4,5-Diaminothieno[2,3-b]pyridine D₂

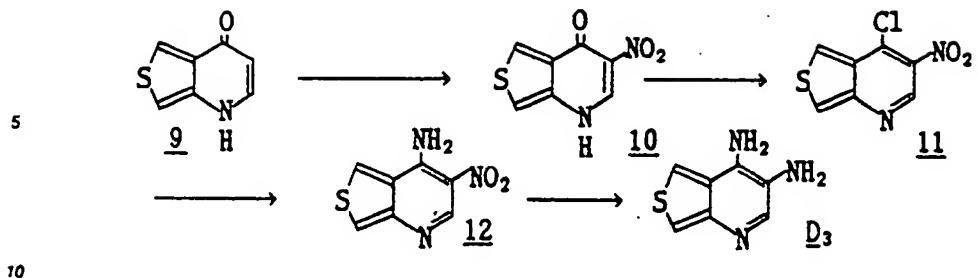
A mixture of 2.57 g of 4-amino-5-nitrothieno[2,3-b]pyridine 8 and 11.1 g of stannous chloride in 240 ml of ethanol is stirred at 75°C for 3 hours. The reaction mixture is treated with activated charcoal and filtered. After concentration of the filtrate, the residue is taken up in ethyl acetate and suspended in 185 ml of 5% aqueous sodium bicarbonate. The organic layer is extracted with dilute hydrochloric acid. The aqueous layer is treated with activated charcoal and filtered. The filtrate is basified to pH = 10 with 10% sodium hydroxide and extracted with ethyl acetate. The extract is dried over magnesium sulfate and evaporated *in vacuo*. The residue is recrystallized from ethyl acetate -ether to afford 1.65 g (76%) of Compound D₂ as pale yellow crystals melting at 159 -160.5°C.

Anal. Calcd. (%) (for C₇H₈N₂S•1/8H₂O)

: C, 50.20; H, 4.36; N, 25.09.

Found (%): C, 50.54; H, 4.24; N, 24.95.

55 Referential Example 5



(1) 3-Nitrothieno[3,4-b]pyridin-4(1H)-one 10

To a suspension of 4.00 g of thieno[3,4-b]pyridin-4(1H)-one **9** in 120 ml of acetic acid is added 3.00 g of nitric acid ($d = 1.38$). The reaction mixture is stirred at 70°C for 3 minutes and cooled to room temperature. The resulting crystals are collected by filtration, and then washed with water and methanol - ether , affording 2.51 g (48%) of Compound **10**. An analytical sample is recrystallized from dimethylsulfoxide -methanol to give yellow crystals melting at 329 -332°C.

Anal. Calcd. (%) (for C₁₂H₁₄N₂O₂S)

C, 42.85; H, 2.05; N, 14.27.

²⁰ Found (%): C. 42.75; H. 2.30; N. 14.13.

(2) 4-Chloro-3-nitrothieno[3,4-b]pyridine 11

A mixture of 3.00 g of 3-nitrothieno[3,4-b]pyridin-4(1H)-one **10** and 9 ml of phosphorous oxychloride is stirred at 105°C (bath temperature) for 1 hour and evaporated to dryness *in vacuo*. The residue is taken up in chloroform and washed with aqueous ammonia and water. The organic phase is dried over magnesium sulfate and evaporated. The residue is purified by column chromatography on silica gel. Elution with dichloromethane -ether (50:1 v/v) affords 2.02 g (60%) of Compound **11**. Recrystallization from ether - petroleum ether affords colorless crystals melting at 129–140°C.

Anal. Calcd. (%): (for C₆H₁₀N₂O₂CIS-1/2H₂O)

Anal. Calcd. (%) (for C₁₂H₁₄N₂O₂)

Found (2%) - C. 22.66 H. 1.55 N. 12.72

2

(3) 4-Amino-3-nitrothieno[3,4-*b*]pyridine 12

To a stirred suspension of 1.25 g of 4-chloro-3-nitrothieno[3,4-*b*]pyridine 11 in 37 ml of 2-propanol is introduced anhydrous ammonia at room temperature during 3 hours. The mixture is concentrated in vacuo and the residue is suspended in water with stirring. The crystals are collected by filtration, washed with water and dried to give 1.09 g (96%) of Compound 12. An analytical sample is recrystallized from chloroform -methanol, giving yellow crystals melting at 307 -309°C.

Anal. Calcd. (%) (for C₆H₇N₂O₂S)

C 43.07 H 258 N 21.52

⁴⁵ Found (%): C 42.93; H 2.69; N 21.36

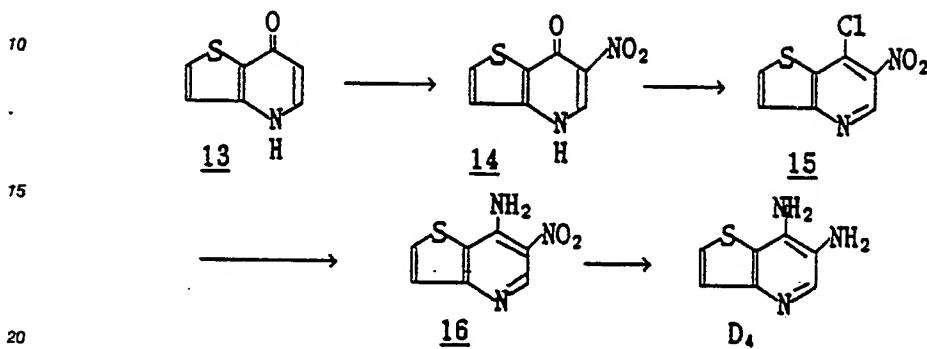
(4) 3,4-Diamino[3,4-*b*]pyridine D.

50 A mixture of 620 mg of 4-amino-3-nitrothieno[3,4-b]pyridine and 3.59 g of stannous chloride dihydrate in 50 ml of ethanol is stirred at 70°C for 1 hour. After evaporation of the solvent in vacuo, the residue is partitioned between ethyl acetate and aqueous sodium bicarbonate. The resulting solid is filtered off and washed with ethyl acetate. The combined extracts are dried and evaporated in vacuo. The residue is purified by column chromatography on neutral alumina. Elution with chloroform -methanol (20:1 v/v) affords 490 mg (93%) of Compound D₁, which is recrystallized from ether -methanol to afford colorless crystals melting at 140 -144°C.

Anal. Calcd. (%) (C₁₂H₁₁N₃S•2/3H₂O)
 : C, 47.44; H, 4.74; N, 23.71.
 Found (%) : C, 47.68; H, 4.85; N, 23.24.

5

Referential Example 6



(1) 6-Nitrothieno[3,2-b]pyridin-7(4H)-one 14

To a solution of 3.1 g of thieno[3,2-*b*]pyridin-7(4H)-one **13** in 90 ml of propionic acid is added 1.5 ml of fuming nitric acid at 110°C with stirring and the mixture is refluxed for 1 hour. The cooled mixture is diluted with 50 ml of ether and the resulting crystals are collected by filtration, washed with water and ether - methanol, and dried to give 3.13 g (78%) of Compound **14**. Recrystallization from dimethyl sulfoxide - methanol affords colorless crystals melting at 328 -331°C (dec.).

30 Anal. Calcd. (%) (for C₁₂H₁₄N₂O₃S) : C, 42.85; H, 2.05; N, 14.27.

Found (%): C, 42.88; H, 2.17; N, 14.21.

35 (2) 7-Chloro-6-nitrothieno[3,2-b]pyridin-7(4H)-one 15

A mixture of 2.7 g of 6-nitrothieno[3,2-b]pyridin-7(4H)-one **14** and 30 ml of phosphorous oxychloride is stirred at 115°C for 1 hour. The reaction mixture is evaporated to dryness *in vacuo*. The residue is taken up in dichloromethane, washed successively with aqueous ammonia and water, and then dried over magnesium sulfate. The solvent is removed *in vacuo* and the crude crystals are purified by column chromatography on silica gel. Elution with dichloromethane - ether (50:1 v/v) affords 2.64 g (90%) of Compound **15**. Recrystallization from ether gives colorless crystals melting at 124 - 125.5°C.

Anal. Calcd. (%) (for C₈H₁₁N₂O₂CIS) : C, 39.17; H, 1.40; N, 13.05.
45 Found (%) : C, 38.96; H, 1.70; N, 12.92.

(3) 7-Amino-6-nitrothieno[3,2-b]pyridine 16

To a suspension of 2.55 g of 7-chloro-6-nitrothieno[3,2-b]pyridine 15 in 130 ml of 2-propanol is introduced excess anhydrous ammonia at 45°C (bath temperature) during 4 hours and the mixture is evaporated in vacuo. The residue is suspended in water, collected by filtration, and then washed with water and ether to give 2.30 g (99%) of Compound 16. An analytical sample is recrystallized from chloroform-methanol, affording yellow crystals melting at 266–268.5°C.

Anal. Calcd. (%) (for C₈H₁₀N₂O₂S)
 : C, 43.07; H, 2.58; N, 21.52.
 Found (%) : C, 43.02; H, 2.76; N, 21.46.

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 (4) 6,7-Diaminothieno[3,2-b]pyridine D.

A mixture of 2.3 g of 7-amino-6-nitrothieno[3,2-b]pyridine 16 and 12.5 g of stannous chloride dihydrate in 160 ml of ethanol is heated with stirring at 70°C for 3 hours. The mixture is evaporated in vacuo and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate. The resulting solid is filtered off and washed with ethyl acetate. The combined extracts are dried and evaporated in vacuo. The residue is purified by column chromatography on silica gel. Elution with chloroform -methanol (10:1 v/v) affords 1.91 g (97%) of Compound D, which is recrystallized from methanol -ether to give colorless melting at 157-159°C.
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 15 Anal. Calcd. (%) (for C₈H₁₀N₂S•1/4H₂O)
 : C, 49.54; H, 4.45; N, 24.76.
 Found (%) : C, 49.79; H, 4.35; N, 24.43.

20 Preparation

25	2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline 10 mg
Wheat starch	48 mg
Magnesium stearate	2 mg

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The above components are mixed each other to prepare a capsule.

35 Effect of the invention

The compounds of the present invention show high affinity to a benzodiazepine receptor. The drugs bound to this receptor are classified as three groups according to the difference of the efficacy. Thus, agonists can be utilized as anxiolytics or anticonvulsants, antagonists can be agents for treating benzodiazepine intoxication and accidental supernumerary uptake, and inverse agonists are expected as psychostimulants.
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Experiments for assessing biological activities of the compounds of the present invention are shown below; the number of the test compound nearly corresponds to the number used in Examples and Tables respectively.

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Experiment 1

Binding test to benzodiazepine receptor

50 This test was carried out in the modified method of Möhler et al. *Science*, **198**, 849-851 (1977). Receptor preparation was provided from the cerebral cortex of Wistar rats (male, 11 to 13 weeks age). Inhibitory action of the test compound on the specific binding of tritium labeled diazepam to the receptor was evaluated as follows. 2nM tritium labeled diazepam and an aqueous solution of the test compound at 5 or 6 concentrations were incubated with the receptor preparation at 0°C for 6 minutes. The 50% inhibitory concentration (IC_{50}) was measured by the concentration-response curve.

55 The inhibitory constant (K_i) was calculated according to the following equation, in which K_d is the dissociation constant of the tritium labeled diazepam and L is the concentration of the labeled ligand.

$$5 \quad Ki = \frac{IC_{50}}{1 + L/Kd}$$

10	Compound No.	Ki (nM)	Compound No.	Ki (nM)
15	C ₂	0.97	C ₅₈	0.525
20	C ₃	15.8	C ₅₉	1.23
25	C ₁₃	8.73	C ₆₀	0.495
30	C ₂₀	27.7	C ₆₁	0.661
35	C ₂₁	1.80	C ₆₇	2.07
40	C ₂₇	1.88	C ₆₈	1.19
45	C ₃₅	19.5	C ₇₀	5.40
	C ₃₈	15.6	C ₇₁	4.57
	C ₄₅	0.582	F ₂	31.8
	C ₄₈	0.97	F ₇	725
	C ₄₉	0.907	K ₆	10.1
	C ₄₉	0.237		

50 Experiment 2

Antagonism of Pentylenetetrazole-Induced Convulsion

Agonistic activity was evaluated in this test. Groups of 8-16 male mice were challenged with a dose of 55 125 mg/kg, s.c. of pentylenetetrazole immediately after intravenous injection of the test compound. The dose required to prevent tonic convulsion and death in 50% of the animal during a 2-h observation period was calculated by the probit method.

	Compound No.	ED ₅₀ (mg/Kg)
10	C ₂	15.97
15	C ₃	2.31
20	C _{1,3}	4.61
25	C _{2,6}	3.90
30	C _{2,11}	2.05
35	C _{2,7}	1.41
40	C _{3,4}	8.52
	C _{4,8}	0.71
	C _{4,9}	1.20
	C _{4,10}	0.59
	C _{4,11}	0.32
	C _{5,9}	3.01
	C _{6,1}	0.74

45 Experiment 3

Potentiation of Pentylenetetrazole-Induced Convulsion

50 Inverse agonist activity was evaluated in this test. Groups of 8-16 mice were challenged with a dose of 90 mg/kg, s.c. of pentylenetetrazole (a subconvulsive dose) immediately after intravenous injection of the test compound. The dose required to produce tonic convulsion and death in 50% of the animal during a 2-h observation period was calculated by the probit method.

5	Compound No.	ED_{50} (mg/Kg)
10	$C_{3,6}$	1.76
15	$C_{5,8}$	1.65
20	$C_{7,1}$	4.18
	F_2	0.13
	K_8	0.54
	F_7	0.50

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Experiment 4

Traction test

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The modified method of Courvoisier et al. (in "Psychotropic Drugs", ed. by S. Garattini & R. Ducrot. p 373. Elsevier Publishing Co., Amsterdam 1957) was employed. Groups of 10 mice were made to hang onto a horizontal metal wire (diameter : 1 mm) by grasping and holding with their forepaws 30 minutes after oral administration of the test compound, and the number of mice gripping the wire with hindpaws within 10 sec was counted. The ED_{50} was calculated by the probit method.

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Experiment 5

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Anticonflict test

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The modified method of Geller and Seifter (Psychopharmacol, 1, 482, 1960) was employed. Groups of 5 or more male Wistar rats with well-established conflict behavior were used. A dose was determined as positive when the number of electric shocks (punishment) exceeded more than 12 during a 1-hour observation period starting 30 minutes after oral administration of the test compound. The ED_{50} was calculated by the probit method.

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5 No.	Compound	Anti-conflict activity ED ₅₀ (mg/kg)	Traction Test ED ₅₀ (mg/kg)
10 C ₄₈	2.68	> 200	
C ₄₈	1.80	> 200	
15 C ₄₉	1.19	> 200	
Diazepam	1.05	5.06	

20 The pharmacological activities described above suggest that the dissociation of anxiolytic action and muscle relaxation action, both being specific to drugs of benzodiazepine type, was achieved. Thus, the compound of the present invention can be an anxiolytic drug not accompanying with a side effect such as dizziness.

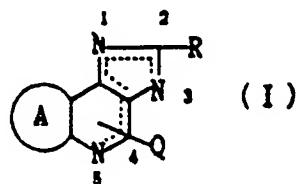
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Claims

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1. A compound of the formula:

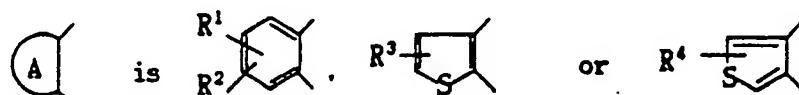
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wherein R is phenyl optionally substituted by one or two of trifluoromethyl, C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ alkylthio, nitro, amino, C₁-C₃ alkanoylamino and C₁-C₃ alkoxy carbonyl, or a 5-or 6-membered heterocyclic group optionally substituted by one or two of halogen, C₁-C₃ alkyl and C₁-C₃ alkoxy; Q is hydrogen, C₁-C₃ alkyl, C₁-C₃ acyl, C₁-C₃ alkylsulfonyl or C₁-C₃ arylsulfonyl,

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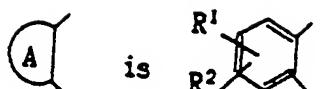


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R¹, R², R³ and R⁴ are each independently hydrogen, halogen, C₁-C₃ alkyl, C₁-C₃ alkoxy or C₁-C₃ haloalkyl; Q is present on the nitrogen atom at the 1, 3 or 5-position, and the dotted line indicates the presence of three double bonds at the position of 2, 3; 3a, 3b; 4, 5/1, 3b; 2, 3; 3a, 4/ or 1, 2; 3a, 3b; 4, 5

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2. A compound as claimed in Claim 1, wherein



5 3. A compound as claimed in Claim 1 or Claim 2, wherein R is a 5-membered heterocyclic group
 optionally substituted by one or two of halogen, C₁-C₃ alkyl and C₁-C₃ alkoxy, e.g. 2-thienyl or 3-methyl-5-isoxazolyl.

10 4. 7-Chloro-2-(2-thienyl)-1H-imidazo[4,5-c]quino line;
 2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline;

15 7-fluoro-2-(3-methylisoxazol-5-yl)-1H-imidazo [4,5-c]quinoline; or
 8-fluoro-2-(3-methylisoxazol-5-yl)-1H-imidazo [4,5-c]quinoline.
 5. A compound as claimed in any one of claims 1 to 4 which is as an acid addition salt thereof.

6. A process for preparing a compound as claimed in Claim 1, which comprises reacting a compound
 of the formula:



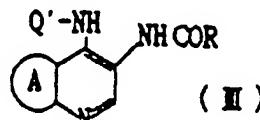
25 wherein Q' is hydrogen or C₁-C₃ alkyl and

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is as defined in Claim 1, with an acylating agent to give a compound of the formula:

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wherein

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, Q' and R each is as defined in Claim 1 and cyclizing the compound (III), and when Q is hydrogen, applying the cyclized product to alkylation, acylation or sulfonylation, if necessary.

55 7. A pharmaceutical or veterinary formulation comprising a compound as claimed in any one of claims 1 to 5 formulated for pharmaceutical or veterinary use, respectively, optionally in unit dosage form and/or further comprising a pharmaceutically or veterinarily acceptable carrier, diluent or excipient.

8. A compound as claimed in any one of claims 1 to 5 or a compound which has been prepared by a process as claimed in claim 6, for use in the treatment of disease.

9. The use of a compound as claimed in any one of claims 1 to 5 or a compound which has been prepared by a process as claimed in claim 6, for the manufacture of a medicament for the treatment of anxiety or depression.

10. A method of making a pharmaceutical or veterinary formulation which comprises mixing a compound as claimed in any one of claims 1 to 5 or a compound which has been prepared by a process as claimed in claim 6, with a pharmaceutically or veterinary acceptable carrier, diluent or excipient.

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EUROPEAN SEARCH REPORT

Application number

EP 86 30 8087

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D, A	EP-A-0 145 340 (RIKER LABORATORIES, INC.) * claims 1, 15, 16 *	1, 2, 6 8	C 07 D 471/04 C 07 D 495/14 A 61 K 31/47 // (C 07 D 471/04 C 07 D 235:00 C 07 D 221:00 (C 07 D 495/04 C 07 D 333:00 C 07 D 235:00 C 07 D 221:00
A	--- CHEMICAL ABSTRACTS, vol. 94, no. 7, 16th February 1981, page 570, column 2, abstract no. 47216f, Columbus, Ohio, US; M.M. ABBASI et al.: "Base induced cyclization of some quinolines. Formation of fused nitrogen heterocyclic ring system", & MONATSH. CHEM. 1980, 111(4), 963-969 (Cat. D,A)	1, 2, 6	
P, A	--- DD-A- 238 235 (CIBA-GEIGY AG) * page 6, formulae 1A, 1B; page 9, formula III; page 10, formula VI; page 11, formulae VIB, VIC *	1, 2	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
	-----		C 07 D 471/00 C 07 D 495/00
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
BERLIN	13-01-1987	HASS C V F	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone			
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